CONTENTS

CONTENTS

INDEX OF CONTRIBUTORS

INDEX

Adrenal cortico-genital syndrome, and a comparison with that of the pituitary basophilic, 29; clinical conditions common to both, 31.

Alkalis, some observations on the aetiology and effect of, on the nephrotic syndrome, 1.

Asthma, hypochlorhydria in, with special reference to the age incidence, 397.

Auricular component of the first heart-sound, 139.

Auricular systole, sounds and murmurs produced by, 139.

Blood in malignant hypertension, an attempt to demonstrate a pressor substance in, 179.

Blood pH and lactic acid in different types of heart disease, 407.

Blood-serum, effect of iodide upon the Wassermann reaction of, 263.

Chicken-pox, tuberculin allergy in, 217.

Diabetes mellitus, a comparison of various diets in the treatment of, 277.

Diabetic coma, secretion of urine in, 53.

Diets of rheumatic families, 228.

Diets, various, a comparison of, in the treatment of diabetes mellitus, 277.

Diphtheria, tuberculin allergy in, 218.

Gallop rhythm, 149; types of triple rhythm, 149; physical basis of, 156.

Haemochromatosis, 121; content of the tissues in iron and sulphur, 121; results of spectrographic examination with especial reference to copper and calcium, 125.

Heart disease, different types of, blood pH and lactic acid in, 407.

Hypertension, malignant, an attempt to demonstrate a pressor substance in the blood in, 179.

Hypochlorhydria in asthma, with special reference to age incidence, 397.

Hysterias, conversion, 429.

Iodides, observations on the therapeutic use of, 247; intolerance to, 254; effect of, on *T. pallidum* and the primary chancre, 256; effect of, on secondary manifestations, 256; action of, on tertiary skin and subcutaneous manifestations, 257; effect of, on certain other tertiary symptoms and signs, 262; effect of, in latent syphilis, 262; effect of, on the Wassermann reaction of the blood-serum, 263.

Iodism, 254.

Lactic acid, and blood pH, in different types of heart disease, 407.

Laurence-Moon-Biedl syndrome, 93.

Lipoid-granulomatosis with defects in the bones, exophthalmos, and diabetes insipidus, 37.

Lymphogranuloma, primary, of the stomach, 81.

Manifestations, secondary, effect of iodide upon, 256.

Manifestations, subcutaneous, action of iodide on, 257.

Measles, tuberculin allergy in, 205.

Mitral stenosis, crescendo murmur of, 142.

Neoplasia, intrathoracic, incidence of, in the teaching hospitals of Great Britain 1894–1928, 321.

Nephrotic syndrome, some observations on the aetiology and effect of alkalis on, 1.

Neuroses, some types of respiration in, 427; anxiety neuroses, 427; conversion hysterias, 429; incidence of respiratory neurosis, 430.

Nitrogen, non-protein, with the plasma proteins, and the sedimentation rate in chronic rheumatic disorders, 269.

Obesity, hypogenitalism, mental retardation, polydactyly, and retinal pigmentation: the Laurence-Moon-Biedl syndrome, 93.

pH, blood, and lactic acid in different types of heart disease, 407.

Parathyroid hormone in man, influence of infection on the action of, 131.

Pellagra, secondary, 191.

Pituitary basophilic syndrome and the adrenal cortico-genital syndrome, a comparison of, 23; clinical conditions common to both, 31.

Pressor substance in the blood in malignant hypertension, an attempt to demonstrate a, 179.

1

616.61–002.26
615.732.235

SOME OBSERVATIONS ON THE AETIOLOGY AND EFFECT OF ALKALIS ON THE NEPHROTIC SYNDROME [1]

By R. B. HAWES and E. C. VARDY

(From King Edward VII College of Medicine, Singapore)

THE following notes of certain observations of the nephrotic and nephroso-nephritic syndromes, made at Tan Tock Seng Clinic in Singapore, describe an attempt to investigate the cause of nephrosis, a condition common in our clinic. It was suggested by certain papers that have recently appeared that the underlying cause in nephrosis is often ankylostomiasis (1) or quartan malaria (2, 5, 6), and by our own observations of the greater prevalence of the nephrotic and nephroso-nephritic syndromes among the poorer classes of our Asiatic population, for whom poor food, unbalanced diets, and even semi-starvation are always important factors, an even poorer class than that which supplies most of the acute beri-beri cases. Beri-beri is easily distinguished both clinically and *post mortem* from nephrosis, which again appears to have no relation to starvation oedema.

Aetiology

The first point to be settled was, what constitutes a case of nephrosis. The paper by Louis Leiter (3) appeared to us to define nephrosis as it is now generally regarded. In this paper Leiter states that there are, as well as important positive findings, equally as important negative ones. The positive findings are albuminuria, with subcutaneous oedema, fluid in the serous cavities, scanty urine, waxy pallor, a typical urinary sediment, a good renal concentration ability, decreased protein, and an increased cholesterol content of the plasma and serum. The negative findings are absence of haematuria, no increase of blood-pressure, no cardiac enlargement, and no uraemic symptoms.

When, however, red blood cells were found in the urine in addition, we classified the case under the nephroso-nephritic syndrome, as we consider their presence in the urine to indicate the presence of inflammatory changes as well as tubular degeneration in the kidney.

To carry out the first part of our investigation, we have tabulated our admissions over a period of forty-two months (November 1929 to April 1933)

[1] Received February 26, 1934.

B

of patients who, on the routine examination, showed oedema with albuminuria not of cardiac or chronic nephritic origin. The cases are quite unselected except for these two conditions. In all cases the site of the oedema has been noted, the blood-pressure, the presence of albumin, red blood cells and types of casts in the urine, the blood urea, the Wassermann reaction, the presence or absence of ova in the stools, and the total red-blood cell count. Thick and thin blood films have also been repeatedly searched for malarial parasites. In most cases, wherever it was thought necessary, the total proteins and cholesterol estimations of the plasma and urea concentration tests have also been carried out.

Attention is therefore drawn to the tabulated list of patients (see Table I). In the table there are forty-three cases recorded. Seventeen cases show more or less the essentials of the nephrotic or nephroso-nephritic type of syndrome, as we understand it. They are cases numbered 3, 6, 8, 12, 16, 19, 20, 26, 27, 28, 29, 30, 33, 39, and 43. Thirteen cases had ankylostomiasis, numbered 2, 9, 11, 13, 18, 22, 24, 27, 32, 36, 38, 40, and 41. Three cases had malaria (two subtertian, one quartan), numbered 1, 9, and 38. Five cases had lues, numbered 1, 19, 31, 38, and 42.

Taking the thirteen cases with ankylostomiasis we find that there was only one case which corresponded with any of the cases numbered under the nephrotic syndrome, that is, Case 27, and it is of interest to note that this patient was a Javanese (1). Cases numbered 11, 24, 36, and 41 had ankylostoma ova in the stools and also a high cholesterol content of the plasma, which suggests, if taken alone, a possible nephrotic lesion. But it will also be noted that there were red blood cells in the urine and that the urea concentration tests were poor.

In the same way on examining the malaria cases we find that none of them correspond with either of the syndromes under investigation. The cases numbered 1 and 9 show some kidney damage as indicated by poor kidney function tests and the presence of red blood cells in the urine. Case 38 had a good kidney function, no red blood cells in the urine, but there was no hypercholesterolaemia. Lastly, it appears that the syphilitic cases cannot be linked with the nephrotic cases. Cases 1 and 42 show signs suggesting a nephritic kidney. Cases 19 and 31 can be classified under the nephrosonephritic syndrome and have also positive Wassermann reactions.

Therefore we have failed to establish either ankylostomiasis or malaria as a common factor in the cause of nephrosis.

Further Investigations in a Later Series of Nephrotic Cases

The second part of our inquiry was suggested by the fact that the majority of cases of nephrosis occurred in poor and underfed Chinese labourers. Limiting our research to the nephrotic syndrome, although in some cases we noticed a gradual degeneration into the nephroso-nephritic or

even the nephritic type of case, we felt that, in a number of cases at least, the condition of nephrosis was not one of primary kidney disease, conforming to Epstein's opinion.   We therefore decided to investigate the effect of dietetic measures and the action of mineral salts on the condition.

The observations that follow may be considered as almost a continuation of those of Osman (4), but on our cases the alkaline mixture of sodium and potassium salts was often ineffective, and uniform results were obtained only with potassium salts alone.   No toxic symptoms were observed, except in those cases that showed red blood cells in the urine, and these were headache and increasing blood-pressure.

Many different forms of treatment were tried, including chlorophyll (fresh acetone extracts and proprietary preparations), high protein diet, diuretics (urea, &c.), thyroid gland (11), green vegetables, concentrated anti-infective Vitamin A, before it was found that very simple dietetic measures prevented deaths.   The oedema, however, was often very persistent, and it was not until we had developed the proper use of the alkaline ash diet with potassium salts that we overcame this difficulty.

It is quite well known that the acid-forming and base-forming qualities of the food influence the course of nephritis.   Sansum, Blatherwick, and Smith (7) have seen marked improvement follow the use of diets which have the base-forming characteristic, and so with the help of tables (8, 9, 10) we have worked out the following basic and acid diets suitable for poor class Chinese patients.

The diets are as follows.   *Basic diet*: 7 a.m. milk, 4 oz.; 10 a.m. rice, 6 oz.; meat, lean, beef or mutton, 4 oz.; potatoes, 8 oz.; green vegetables, 8 oz. (cabbage, lettuce, spinach); orange, 1; bananas, 2; 4 p.m. repeat 10 a.m.; 6 p.m. and 8. p.m. milk, 4 oz.   Caloric value, P. 90, C. 148, F. 35·2 = Cal. 1288 + 726 (rice) = *2014* and a basic value of 10·16.   *Acid diet* (used for control cases): 7 a.m. Chinese tea, with bread and butter; 10 a.m. rice, 9 oz.; meat, 4 oz.; hen eggs, 2; lettuce, 4 oz.; oranges, 2; bread and butter; 4 p.m. repeat 10 a.m.; 6 p.m. and 8 p.m. Chinese tea, bread and butter.   Total bread per day, 4/5 lb.; total butter per day, 3 oz.   Caloric value, P. 100, C. 199·6, F. 155·8 = Cal. 2247 + 1020 (rice) = *3267* and an acid value of 65·54.   Both diets are salt-free except for the small amounts in the bread and meat.

On admission the patients were put on a low milk diet for a few days, during which period they settled down, and the following special investigations were carried out:

1. *The extent of and sites of the oedema*: the patient weighed.   2. *Urine examination*: kidney function tests, albumin percentage, sugar, bile, casts, and cells.   3. *Physical examination*: heart, blood-pressure, lungs, abdomen, central nervous system, fundi.   4. *Blood examination*: total proteins, albumin, globulin, non-protein-nitrogen, urea, cholesterol, chlorides, and calcium.

The patient was then put on to the selected diet.   With the basic diet he was given potassium salts.

TABLE II

No.	Age	Nationality.	Oedema.	Blood-pressure.	Urine alb.	Urine Casts.	Red cells.	Blood urea mg.	Stools ova.	Total proteins grm.	Alb.	Glob.
1	28	Kheh	Legs, face	105/85, 120/80	+	H. G.	few	23	0	N.R.	N.R.	N.R.
2	40	Cantonese	General	150/105, 200/180	++	G. (few)	few	50	Ank.	6·1	5·8	N.R.
3	40	Hokien	Legs, face scrotum	130/80, 120/90	++	H. G.	0	100	0	N.R.	N.R.	N.R.
4	30	Hylam	General	110/74, 90/76	++	G. (many)	0	45	0	3·18	2·18	0·89
5	32	Kheh	Feet, legs	158/96, 128/84	++	G. H.	+	101	0	N.R.	N.R.	N.R.
6	33	Hylam	Legs, feet, face	110/80, 115/85	++	G. H.	0	N.R.	0	N.R.	N.R.	N.R.
7	34	Hokien	General	164/120	++	G. H.	few	20	0	3·98	2·65	0·49
8	45	Hokien	Legs, feet	110/48	++	G.	0	44·5	0	4·28	2·09	0·87
9	31	Cantonese	General	110/80	+	G. H.	few	31	Ank. Tric.	N.R.	N.R.	N.R.
10	27	Hokien	General	180/80, 125/90	+	Nil.	few	12	0	N.R.	N.R.	N.R.
11	17	Eurasian	Legs, feet, face	134/90	+	G. H.	+++	30	0 Ank.	N.R.	N.R.	N.R.
12	19	Teochew	Legs, feet	126/88	+	G. H.	few	19	0	3·5	N.R.	N.R.
13	36	Hylam	General	125/90	+	G. H. E.	0	39	Ank.	N.R.	N.R.	N.R.
14	27	Teochew	Legs, face	108/66, 116/90	+++	0	0	40	0	N.R.	N.R.	N.R.
15	25	Cantonese	General	118/92	+	H.	+	48	0	N.R.	N.R.	N.R.
16	?	Chinese	Legs	110/80	++	G. H.	0	26	0	N.R.	N.R.	N.R.
17	32	Cantonese	Legs, feet	110/85, 105/75	+	G.	+	29	0	N.R.	N.R.	N.R.
18	30	Hokien	General	120/80	++	H.	0	33	Ank.	3·2	N.R.	N.R.
19	27	Hokien	Legs, feet	130/90, 120/70	++	G. H.	+	25	0	4·49	N.R.	N.R.
20	18	Kheh	General	90/60, 110/60	++	H.	0	62	0	N.R.	N.R.	N.R.
21	32	Cantonese	General	120/80	++	G. H.	0	28	0	N.R.	N.R.	N.R.
22	30	Hengwha	Feet	142/96	++	H. G.	0	60	Ank.	4·9	4·7	N.R.
23	27	Teochew	General	120/75	+	G. H.	0	40	0	4·9	2·65	1·53
24	35	Cantonese	General	125/95, 132/82	++	H.	++	49	Ank. Tric.	6·28	4·77	0·20
25	25	Tamil	General	204/134	++	H.	+	66	0	5·18	4·50	N.R.
26	42	Teochew	General	122/80	++	G. H.	0	39·2	0	4·82	4·08	0·26
27	30	Javanese	General	160/60	+	G. H.	0	27	Ank. Tric.	4·8	2·4	0·5
28	56	Cantonese	General	140/100	++	G.	0	52	0	4·88	3·82	0·31
29	41	Teochew	Legs, feet	142/108	+	G. E.	+	37	0	5·80	4·37	0·36
30	36	Hokien	General	148/96	++	H.	+	20	0	5·5	4·54	0·11
31	29	Cantonese	General	N.R.	+	H. E.	+++	27	0	4·4	0·35	1·38
32	16	Hylam	General	100/85	+	G. H.	0	36	Ank.	6·46	5·29	0·14
33	13	Hylam	General	100/20	+	H.	0	N.R.	Tric.	N.R.	N.R.	N.R.
34	38	Hylam	General	130/87	+	G. H.	0	105	0	2·33	1·53	0·51
35	15	Cantonese	Legs, face, abdomen	146/122	+++	G. E. H.	0	68	Tric.	N.R.	N.R.	N.R.
36	28	Hokien	Face, legs, body	112/90	+	G. E. H.	+	40	Ank.	2·87	1·67	0·37
37	24	Cantonese	Legs, feet	150/78	++	H. G.	0	34	0	6·3	3·9	1·1
38	33	Kheh	General	128/96	++	G. H.	0	50	Ank.	5·52	3·23	1·62
39	21	Teochew	General	114/78	+	E.	+	35	0	4·61	3·55	0·4
40	28	Kheh	General	116/84	+	G. H.	0	75	Ank.	N.R.	N.R.	N.R.
41	23	Hokien	General	112/84	+	G. H.	+	33	Ank.	5·65	1·9	0·65
42	28	Kheh	Face, limbs	118/75	+	0	few	12	0	N.R.	N.R.	N.R.
43	29	Kheh	Legs, body	108/70	+	G.	few	22	0	N.R.	N.R.	N.R.

H = hyaline; G = granular; E = epithelial; Ank. = ankylostoma; Tric. = trichiuris; N.R. =

Alb.	Glob.	Cholesterol.	Other diseases.	Heart.	Urea concentration. %	R.B.C. millions.	W.B.C.	Remarks.
N.R.	N.R.	N.R.	Syphilis, S.T. malaria	Rapid, normal size	1·85, 1·75, N.R.	3·7	7,187	Some kidney damage
8	N.R.	131, 207	Ank.	Not enlarged	1·4, 1·6, 1·6	2·2	4,000	Some kidney damage
N.R.	N.R.	612	0	Normal	2·0, 2·5, N.R.	1·5	1,872	Nephrotic synd.
18	0·89	127, 100	0	Enlarged	1·14, 1·48, N.R.	3·9	7,600	Some kidney damage
N.R.	N.R.	N.R.	0	Enlarged	N.R.	1·9	5,625	—
N.R.	N.R.	319	0	Rt. side enlarged	2·0, 2·5, N.R.	1·5	15,000	Suggests a nephrotic synd.
65	0·49	120	0	Normal	N.R.	N.R.	N.R.	—
09	0·87	434·7	Old hemiplegia	Enlarged	1·48, 2·5, 2·6	N.R.	N.R.	Nephrotic synd.
N.R.	N.R.	N.R.	S.T. malaria Ank., Tric.	Normal	0·75, 0·8, N.R.	5·0	2,200	Some kidney damage
N.R.	N.R.	N.R.	0	Normal	N.R.	4·0	9,200	—
N.R.	N.R.	N.R.	Ank.	Normal	2·14, 2·45, 2·5	N.R.	11,250	Unfortunately not fully investigated, kidney funct. good
N.R.	N.R.	483	0	Normal	N.R.	2·5	N.R.	Nephroso-nephritic synd.
N.R.	N.R.	N.R.	Ank.	Normal	N.R.	4·9	5,800	—
N.R.	N.R.	N.R.	Diarrhoea	Normal	N.R.	4·8	7,344	—
N.R.	N.R.	N.R.	0	Normal	1·45, 2·0, 2·4	N.R.	N.R.	—
N.R.	N.R.	425	0	Normal	1·3, 1·9, 2·5	4·0	9,000	Suggests a nephrotic synd.
N.R.	N.R.	300, 382	0	Normal	3·15, 3·15, 2·6	3·7	8,437	Nephroso-nephritic synd.
N.R.	N.R.	137	Ank.	Normal	1·5, 2·36, 2·6	N.R.	N.R.	Ank., good kidney funct., normal cholesterol
N.R.	N.R.	505	Syphilis	Normal	2·8, 2·9, 3·0	2·8	4,500	Nephroso-nephritic synd., syphilis
N.R.	N.R.	555	0	Normal	2·1, 2·6, 2·1	4·0	6,500	Nephrotic synd.
N.R.	N.R.	N.R.	0	Normal	1·55, N.R., N.R.	2·1	7,000	—
7	N.R.	111·9	Ank.	Enlarged	1·9, 1·95, 1·8	4·9	4,000	Ank., poor kidney funct., normal cholesterol
65	1·53	157	0	Normal	N.R.	N.R.	N.R.	—
77	0·20	561	Ank.	Enlarged	1·2, 1·3, 1·4	2·2	6,000	Ank., poor kidney funct., high cholesterol but R.B.C. in urine and signs of nephritis
50	N.R.	214	0	Enlarged	0·98, 1·6, 1·18	N.R.	N.R.	—
08	0·26	315	0	Normal	2·8, 4·6, 3·2	4·7	6,500	Nephrotic synd.
4	0·5	405	Ank.	Normal	1·1, 2·4, 2·2	3·7	6,000	Javanese ank., with a nephrotic synd.
82	0·31	344, 647	0	Normal	2·0, 2·9, N.R.	3·5	2,680	Nephrotic synd.
37	0·36	545	0	Normal	2·1, 2·4, 2·2	N.R.	N.R.	Nephroso-nephritic synd.
54	0·11	357	0	Normal	1·8, 2·05, 2·5	4·0	10,000	Nephroso-nephritic synd.
35	1·38	429	Syphilis.	Normal	1·5, 1·8, 2·5	3·7	6,256	Syphilis, good kidney funct., high cholesterol but R.B.C. in urine
29	0·14	176	Ank.	Enlarged	N.R.	5·2	7,000	Ank., cholesterol normal
N.R.	N.R.	545	Tric.	Enlarged	N.R.	N.R.	8,000	Tric., cholesterol high, possible nephrotic synd.
53	0·51	170	0	Normal	N.R.	2·8	12,000	—
N.R.	N.R.	N.R.	Tric.	Normal	N.R.	5·6	19,687	—
67	0·37	230	Ank.	Normal	2·4, 2·1, 1·8	3·5	8,500	Ank., cholesterol high but R.B.C. in urine
9	1·1	145	0	Normal	0·88, 1·1, 1·5	4·5	5,600	
23	1·62	150	Q. malaria, Syphilis, Ank.	Normal	1·28, 1·9, 2·4	3·0	6,500	Malaria, syphilis, ank., kidney funct. good, cholesterol normal
55	0·4	468	0	Normal	2·5, 3·1, 3·2	3·4	10,600	Nephroso-nephritic synd.
N.R.	N.R.	150	Ank.	Normal	1·98, 1·92, 1·86	5·6	8,000	Ank., poor kidney funct., normal cholesterol
9	0·65	322, 483	Ank.	Normal	1·22, 1·66, 1·67		6,500	Ank., poor kidney funct., cholesterol high, signs of kidney inflammation
N.R.	N.R.	N.R.	Syphilis	Normal	1·6, 1·6, 1·8	2·5	4,010	Syphilis with kidney damage
N.R.	N.R.	625, 503	0	Normal	3·05, 2·4, 2·5	4·1	6,562	Nephroso-nephritic synd.

urus N.R. = not recorded ; synd. = syndrome ; funct. = function.

Potassium bicarbonate. . . . . . $\Big\}$ āā gr. xxx
Potassium citrate. . . . . . .
Aqua ad . . . . 1 oz.

at first thrice daily, later three-hourly, two-hourly, and in some cases one-hourly, the idea being to push these salts in an endeavour to make the urine alkaline within forty-eight hours. Once the urine is alkaline and the daily output of urine increasing with a consequent decrease in the weight of the patient, the salts are administered in gradually decreasing amounts and eventually given in just sufficient doses to keep the urine alkaline. With the acid diet ammonium chloride is combined (gr. xv thrice daily is usually enough). During these alkaline or acid periods the rise or the fall of the oedema, the output of urine, and its reaction and weight of the patient were noted daily. The albumin percentage is estimated on twenty-four hours' specimen by Esbach's method daily, every third day, or weekly, depending upon the progress of each individual case.

At this time if any foci of infection such as alveolar abscesses or infected sinuses were found they were attended to, or if, on the other hand, malaria, ankylostomiasis or lues were present, they were also treated.

After we had been trying this dietetic treatment for some time we eventually realized that three beneficial results were emerging from out of what at first appeared to be an endless series of failures. These were: (1) diminution of the oedema; (2) lowering of the hypercholesterolaemia; and (3) some control of the albumin output in the urine; and these results were being obtained while the patients were on the alkaline ash treatment, and when the treatment was changed to the acid side the reverse was generally noted.

To illustrate these three points more clearly we have shown three groups of cases, each group concerned separately with one of these three points, and finally a fourth group in which we have demonstrated the three factors together in each case.

Group 1, the oedema (Cases 1 to 4). Basic diet was commenced and potassium salts pushed until the urine became alkaline as described above, the patients began to lose their oedema, their urine output increased, and their weight diminished. Sometimes at the beginning of the alkaline period the condition appeared to become worse for a few days, but later settled down. Usually the subcutaneous fluid was lost first, and later the serous cavities emptied themselves. During the acid-control periods the improvement noticed while the patient was undergoing the alkaline treatment was arrested, and in some cases a return of the oedema, &c., was seen.

Group 2, hypercholesterolaemia (Cases 2, 4, 5, and 6). Patients who were on the alkaline treatment very quickly showed a fall in their plasma cholesterol which usually soon was within normal limits, while a return to the acid diet caused an increase.

Group 3, albuminuria (see Table II). We now come to the most difficult and disappointing stage of the investigation, and beyond a certain point we

have been unable to proceed.   One of the main features of a case of nephrosis is the enormous daily output of albumin in the urine ; the amount is often so great that by the Esbach's albuminometer the percentage figures range between 0·5 per cent. to 1·8 per cent. or even 2 per cent.   The urine of all our cases on admission was loaded with albumin, the average percentage being in the neighbourhood of 1·0 per cent.   The lowest was 0·09 per cent. and the highest 1·6 per cent.   It was soon noticed, during the alkaline periods, that the albumin percentage reports were being returned from the laboratory as 'no deposits in 24 hours'.   If the patient was then changed over to the acid side, the albumin percentage figure again began to rise. At this stage it was thought that a 'cure' for nephrosis had been discovered, but on examining the urine more closely (Esbach's method at its best yields only approximate results) it was found that if Heller's nitric-acid test was carried out traces of albumin were still present in the urine. Because it was thought that the control of the albumin wastage during the basic treatment might perhaps be due to the fact that the patient was in an alkaline condition rather than to any possible action of the potassium salts, we decided to carry out yet a further experiment, and four cases, all of whom had, in the untreated stage, very high albumin percentage figures, were selected.   All these were given the alkaline diet, two cases being given potassium salts and two sodium salts.   The results of this are shown in Table II, from which it will be noticed that benefit was apparent only when potassium salts were being used, and this was not due to dilution of the albumin concentration by diuresis caused by these salts, but a great diminution in the total daily quantity excreted.

Group 4 (Cases 7, 8, 9).   In this group there are three cases all at the beginning representing the clinical and laboratory picture of nephrosis. They were first put on to the acid control and all went farther downhill. On changing over, however, to potassium salts, the state of affairs gradually altered, and these cases are now in a semi-cured condition, namely, oedema-free, with normal plasma cholesterol and controlled albumin output (i.e. only a trace with Heller's test).

Unfortunately a trace of albumin can still always be obtained in these cases if more accurate methods than Esbach's are carried out, except in one case where the albumin completely disappeared for a long period (Case 10).

The subsequent behaviour of these patients is of interest.   Just as the diabetic, on forsaking his special diet and insulin injections once more suffers from thirst, polyuria, and glycosuria, so the nephrotic on discharge from hospital, which is often insisted upon by the patients themselves, or, even under control in hospital, on return to the ordinary Chinese diet with no potassium salts suffers again from oedema and albuminuria.   So long, however, as the special basic régime is followed, the majority remain fit and able to perform various forms of work, and we have in hospital, at the moment of writing, six patients, all of whom are carrying out light work satisfactorily.

Unfortunately there are cases in which the patient, after reaping the

initial benefit of the basic treatment, passes out of the nephrotic stage into
the nephroso-nephritic or even the nephritic state.   This fact encourages us to
believe that there must be at least two factors present in nephrosis, one
dietetic and the other infective or toxic in nature.   It is not possible yet
for us to say that of these two factors the dietetic is the more important,
but in our opinion it is very important indeed.   It is not clear in what way
a fault in the diet assists the infective or toxic factor (although the remark-
able effect of potassium is very suggestive of either a defect in the supply
or absorption of this metal) whether by disorganizing the kidney function as
regards protein retention or by changing protein metabolism, but by what-
ever method it may work if it is allowed to proceed unrestrained, gross
damage to the kidney ultimately results, such as we believe can in most
cases be minimized or even averted by attention to the dietetic factor.

Case Reports

Case 1.   Hospital No. 539.   Male, aged 30 years, born in Hainan.
Admitted 2.2.33.   His people were farmers, and when old enough he
also farmed his father's land.   He could not remember any severe illness
during childhood.   He came to Singapore five years previously, where he
worked as a grass-cutter for one year and then went to Johore and worked
as a rubber-tapper.   His food consisted of rice, a little meat, salt fish, and
some green vegetables weekly.   He lived with forty other men.   He took
no opium and no alcohol, and he had no illness until three to four months
previous, when he noticed a swelling of the legs, feet, and hands which
slowly increased, and he was eventually prevented from working, on account
of his abdominal distension.   There was no history of any other disease.

On admission he was pale with oedema of the face, hands, feet, and
genitals.   There was no fever, headache, cough, or dyspnoea.   His appetite
was good, and he complained only of the discomfort due to oedema.   The
heart was not enlarged, the apex beat was in the fifth interspace, internal to
the nipple, and there was no murmur.   His pulse was 78 and blood-pres-
sure 130/98.   There was fluid at the base of both *lungs*.   Ascites was
moderate, and neither liver nor spleen was palpable.   In the central
nervous system the cranial nerves were intact—motor and sensory functions
were normal.   The reflexes were normal, also the fundi.   The *urine* was
straw coloured—sp. gr. 1028, acid; albumin 0·6 per cent. with no sugar,
bile, or acetone.   In the deposit there were hyaline and granular casts, the
cells were epithelial, and there were no red blood cells.   The *stools* contained
no ova, and there was no sputum.   *Urea concentration test*: fasting 30 c.c.
1·9 per cent.   The first specimen was 42 c.c. 2·4 per cent., the second 38 c.c.
2·8 per cent.   The Wassermann reaction was negative.   *Blood*: Hb 55 per
cent., R.B.C. 4,200,000, W.B.C. 8,500.   Differential: polys. 50 per cent.,
lymphs 42 per cent., eosin 8 per cent.; there were no malarial parasites.
Blood proteins: the total proteins were 6·01 grm. per cent., fibrinogen
1·85 grm. per cent., albumin 2·0 grm. per cent., globulin 2·16 grm. per cent.,
urea 32 mg. per cent., non-protein nitrogen 43 mg. per cent., chlorides
669 mg. per cent., cholesterol 442 mg. per cent.   His *weight* was 136 lb.

Progress and treatment.   The treatment given from 2.2.33 to 3.3.33 was
the ' acid type '.   His weight on 2.2.33 was 136 lb., on 8.2.33. 137 lb., on

27.2.33 134 lb.   On 20.2.33 diarrhoea commenced, and this, we think, accounted for the slight loss in weight, because on 3.3.33 the genitals were enormous, and the general oedema the same after one month's treatment.   The treatment from 3.3.33 to 18.4.33 was 'alkaline'.   His weight on 24.3.33 was 126 lb., on 27.3.33 124 lb., on 3.4.33 120 lb., on 6.4.33 114 lb., and on 18.4.33 106 lb.   Clinically on 18.4.33 there was no oedema except a slight amount of pitting over the pre-tibial areas.

Case 2.   Male, aged 29, was admitted into hospital (No. 5646) on 10.7.33.   This man was born in China and came to Singapore about five years previously.   He worked as a pig-breeder, and later became a shop-keeper.   He did not remember having any other illness.   His diet consisted of rice, a little pork, salt fish, and vegetables, and he occasionally drank brandy.   He noticed the swelling twenty-five days previously, when his feet began to swell first, then his legs, hands, and abdomen.   He had no other complaint.   He was admitted with general anasarca (oedema of the legs, hands, chest, abdominal walls, and sacral regions).   There was no fever, cough, or dyspnoea : his appetite was good and bowels regular.   There was no enlargement of the *heart* and no murmurs.   Pulse 76, blood-pressure 132/86. Fluid was found at both bases of the *lungs*.   There was no sputum, and the tonsils were not enlarged : he had good teeth.   Ascites was present ; the liver and spleen were not palpable.   Central nervous system : the cranial nerves were all intact and motor and sensory functions normal, also fundi. *Stools* : ankylostoma ova were seen in large numbers.   *Urea concentration test* : fasting 30 c.c. 1·9 per cent.   First specimen was 40 c.c. 2·3 per cent., second specimen 39 c.c. 2·7 per cent., and third specimen 2·55 per cent.   *Urine* : albumin (0·4 per cent.).   Casts were granular and hyaline.   Pus and epi-thelial cells present.   *Blood* : Hb 46 per cent., R.B.C. 2,800,000, W.B.C. 6,800.   Differential count : polys. 48·5 per cent., eosin 39 per cent., lympho. 9·7 per cent., mono. 2·8 per cent.   The Wassermann reaction was negative, *Blood proteins* : the total proteins were 4·07 grm. per cent., urea 30 mg. per cent., non-protein nitrogen 30 mg. per cent., cholesterol 352 mg. per cent.

Special Note.   At the commencement of his treatment this patient was given the routine hospital ankylostomiasis treatment ; sixty worms were recovered and the Hb rose to 70 per cent.

Progress and treatment.   From 10.7.33 to 18.7.33 'acid type' treatment was given, and on 14.7.33 the patient had pain in the epigastrium.   Ascites increased, with swollen scrotum, and his legs became very tender and tense. On 18.7.33 his condition was the same and the patient was very uncomfort-able.   On 19.7.33 the treatment was changed to the 'alkaline' type, and on 24.7.33 he felt better, and his face was normal and he moved freely. On 28.7.33 he had oedema of the limbs and abdomen only, and on 9.8.33 there was no oedema.   His weight on 10.7.33 was 148 lb., and on 10.8.33 137 lb. ; finally on 23·9·33 it was 120 lb.

Case 3.   A male, aged 26 years, was admitted into hospital (No. 1402— Hokien) on the 20th March, 1933.   He was born in Fu-Kien, China, was a farmer, and had always enjoyed good health.   He came to Singapore four years previously and worked as a wharf coolie.   His food consisted of rice, meat twice a week, and salt fish twice a week, also green vegetables.   Two and a half months ago he noticed a swelling of the feet and abdomen, which

gradually got worse. There was no breathlessness. Eventually he was unable to work owing to size of legs and abdomen.

On admission he was pale with oedema of the legs and feet, hands, and a little in the face. Ascites was present. There was no fever, headache, cough, or shortness of the breath, his appetite was good and bowels regular. There was no cardiac enlargement and no murmurs. His pulse was 72, blood-pressure 124/82. In the *chest* hydrothorax was present; the upper lobes gave vesicular breathing. The *teeth* were good. Ascites was well marked, and the liver and spleen were not palpable. Central nervous system: cranial nerves all intact and motor power good. The sensations were normal—also the fundi. *Urine*: this was straw coloured with sp. gr. 1004; acid, albumin (1·0 per cent.). There was no sugar, bile, or acetone. In the deposit were epithelial, granular, and hyaline casts. *Cells* were epithelial with no red blood cells. In the *stools* a few ankylostoma ova were seen. There was no *sputum*. *Urea concentration test*: fasting 30 c.c. 1·62 per cent., first specimen showed 40 c.c. 2·28 per cent., second specimen 42 c.c. 2·8 per cent., and the third specimen showed 38 c.c. 2·3 per cent. *Blood*: Hb 60 per cent., R.B.C. 4,010,000, W.B.C. 6,562. Differential count: polys. 87 per cent., large lymph. 1·8 per cent., eosin. 2 per cent., small lymph. 15 per cent. No malarial parasites were seen. The Wassermann reaction was negative and Kahn negative. *Blood protein*: total proteins were 5·06 grm. per cent., albumin 2·97 grm. per cent., globulin 1·08 grm. per cent. fibrinogen 1·01 grm. per cent., urea 35 mg. per cent., non-protein nitrogen 31·5 mg. per cent., cholesterol 297 mg. per cent. The patient's *weight* was 106 lb.

Progress and treatment. Treatment from 20.3.33 to 3.4.33 was the acid régime. On 20.3.33 he weighed 106 lb., on 29.3.33 110 lb., on 3.4.33 the ascites was very much increased, and the other oedematous areas had swollen more, accompanied by a slight rise of temperature. From 7.4.33 to 2.5.33 *alkaline régime.* On 8.4.33 he weighed 110 lb., on 18.4.33 110 lb., on 24.4.33 104 lb., on 26.4.33 98 lb., and on 2.5.33 92 lb. By this time there was no oedema of the feet or face, and no hydrothorax. There was a small amount of fluid in the peritoneal cavity, but the general condition was vastly improved. During the acid régime his albuminuria increased and oedema reappeared, while with the alkaline régime the albumin all but disappeared and the oedema disappeared. On 10.12.33 he completed an alkaline period. His general condition changed beyond all recognition, he was free from oedema, and weighed 111 lb. The albumin percentage in the urine was 0·02 per cent. Plasma cholesterol was 170 mg. per cent. He became active, and was one of the cases working under observation in the wards.

Case 4. A male (Hokien) was admitted into hospital (No. 2942) on 5.6.33. He was 30 years of age, was born in China, where he had worked in a store, came to this Colony eight years previously and worked as a weeder; he was six years in Johore and two on the Island. Ten months previously he had a slight fever with rigors, which lasted three days, the symptoms suggesting a coryza. Two days later there was a swelling of the feet and legs, then of the hands, face, and finally the abdomen became distended. This swelling had slowly increased.

On admission he was suffering from a general anarsaca (face, hands, arms, legs, abdominal walls were oedematous with free fluid in peritoneal and

pleural cavities).   There were no other symptoms.   The *heart* was normal, blood-pressure 108/72, and pulse 66.   *Lungs*: fluid was found at the base of both the lungs, the upper lobes being normal.   Ascites was present, the spleen and liver not palpable.   No abnormality was detected in the central nervous system, reflexes and motor functions were normal.   *Urine* was dark coloured, acid sp. gr. 1040, albumin (0·7 per cent.).   Sugar, bile, and acetone were absent.   In the deposit were granular and hyaline casts, there were epithelial cells but no red blood cells.   *Stools* showed no ova and there was no sputum.   *Urea concentration test*: first specimen was 2·1 per cent., and the second 2·17 per cent., the third was 2·28 per cent.   *Blood*: Hb 88 per cent., R.B.C. 5,990,000, W.B.C. 6,300. Differential count : polys. 80·4 per cent., lympho. 11·3 per cent., eosin. 4·6 per cent., monos. 2·5 per cent. The Wassermann reaction was negative.   *Blood proteins*, : the total proteins were 3·18 grm. per cent., fibrinogen 0·56 grm. per cent., albumin 2·46 grm. per cent. ; globulin 0·19 grm. per cent., urea 40 mg. per cent., non-protein nitrogen 38 mg. per cent., chlorides 855 mg. per cent., calcium 8·1 mg. per cent., cholesterol 625 mg. per cent.

Progress and treatment.   Treatment : on 7.6.33 the patient was put on to the alkaline treatment.   On 8.6.33 his weight was 122 lb., on 4.7.33 112 lb., and on 13.7.33 110 lb.   By this time the oedema gradually decreased, and on 17.7.33 there was no oedema present.   The pleural cavities and abdomen were empty.   After this the patient, due to the fact that he thought he was 'cured', would not co-operate, and repeatedly bought food outside, and hence relapsed time and time again, until finally he was discharged on 18.9.33.

These following cases illustrate the effect of treatment on the plasma cholesterol.

Case 4.   On 5.6.33 his plasma cholesterol was 625 mg. per cent., on 7.6.33 he was put on to the alkaline diet with potassium salts, and on 10.7.33 the figure fell to 330 mg. per cent.   He was discharged on 18.9.33, and at that time his cholesterol was 225 mg. per cent.

Case 2.   On 10.7.33 the plasma cholesterol on admission was 352 mg. per cent.   From 19.7.33 to 1.9.33 he was given the alkaline treatment, and his plasma cholesterol fell to 143 mg. per cent.   From 1.9.33 the acid treatment was given, on 25.9.33 the cholesterol was 185 mg. per cent., and on 30.9.33 it was 204 mg. per cent.   On 30.9.33 the alkaline régime was recommenced, but unfortunately the patient absconded within the next few days.

Case 5.   This Chinese male was admitted into hospital (No. 6281) on 5.11.32, aged 22 years.   His investigation revealed the following : he had been out of work for a considerable period, and two months before admission swelling had commenced in his feet and abdomen.   His urine contained a large amount of albumin, hyaline casts, and epithelial cells.   The urea concentration test was normal.   For two months he had been on a high protein diet with calcium chloride and practically no improvement had been noted. On 20.2.33 his condition was as follows : oedema of the feet, hands, and chest-wall, also fluid in the pleural and peritoneal cavities.   His *heart* was normal and blood-pressure low.   The upper portions of the *lungs* were clear, the spleen and liver were not palpable.   Central nervous system intact, and fundi normal.   *Urine* : acid, albumin (0·8 per cent.), sugar, bile, and acetone

TABLE II

This table of urinary findings shows the effect of the alkaline diet and potassium salts on the degree of albuminuria. Four cases were taken and all at first given the alkaline ash diet with no medicine. Later two of the cases were given potassium salts (citrate and bicarbonate), and two others as control cases, sod. salts (citrate and bicarbonate). The albumin was estimated in Esbach's method and the figures are grm. of albumin per 1000 c.c. of urine.

Case 1

Date.	Medicine.	Reaction.	Alb.	Amount.
				oz.
31.8.33	Nil	Acid	11·5	24
1.9.33	Nil	Acid	5·0	50
2.9.33	Nil	Acid	8·0	48
3.9.33	Pot. salts	Acid	4·0	16
4.9.33	Pot. salts	Alk.	No deposit	24
7.9.33	Pot. salts	Alk.	No deposit	48
8.9.33	Pot. salts	Alk,	0·5	40
9.9.33	Pot. salts	Alk.	No deposit	26
16.9.33	Pot. salts	Alk.	No deposit	26
17.9.33	Nil	Alk.	No deposit	36
18.9.33	Nil	Alk.	No deposit	25
19.9.33	Nil	Alk.	1·0	46
20.9.33	Nil	Acid	3·2	40
21.9.33	Nil	Acid	1·0	36
22.9.33	Nil	Acid	0·5	32
23.9.33	Nil	Acid	5·0	38
24.9.33	Nil	Alk.	0·0	38
25.9.33	Nil	Alk.	0·0	24
26.9.33	Nil	Acid	6·0	20
27.9.33	Nil	Acid	5·0	30
28.9.33	Pot. salts	Acid	1·0	35
29.9.33	Pot. salts	Alk.	0·0	26
30.9.33	Pot. salts	Alk.	0·0	26
1.10.33	Pot. salts	Alk.	0·0	34

Case 2

Date.	Medicine.	Reaction.	Alb.	Amount.
				oz.
31.8.33	Nil	Acid	6·0	20
1.9.33	Nil	Acid	6·0	28
2.9.33	Nil	Acid	2·0	40
3.9.33	Pot. salts	Alk.	0·5	26
4.9.33	Pot. salts	Alk.	0·3	20
5.9.33	Pot. salts	Alk.	1·0	16
6.9.33	Pot. salts	Alk.	0·2	16
7.9.33	Pot. salts	Alk.	No deposit	16
8.9.33	Pot. salts	Alk.	0·5	17
9.9.33	Pot. salts	Alk.	0·45	26
16.9.33	Pot. salts	Alk.	No deposit	40
17.9.33	Pot. salts	Alk.	No deposit	30
23.9.33	Pot. salts	Alk.	No deposit	30

This patient here developed a sore throat, and had a temperature for several days. Red blood cells appeared in his urine, and it appeared as if he was developing a nephroso-nephritic type of lesion as shown by increasing blood-pressure and lowered urea concentration.

TABLE II (*continued*).   *Control Cases*

Case 3

Date.	Medicine.	Reaction.	Alb.	Amount. oz.
31.8.33	Nil	Acid	9·0	22
1.9.33	Nil	Acid	6·0	26
2.9.33	Nil	Acid	12·0	24
3.9.33	Sod. salts	Acid	14·0	22
4.9.33	Sod. salts	Slightly alk.	8·0	22
5.9.33	Sod. salts	Slightly alk.	3·0	24
6.9.33	Sod. salts	Slightly alk.	No deposit	26
7.9.33	Sod. salts	Alk.	No deposit	20
8.9.33	Sod. salts	Alk.	1·0	24
9.9.33	Sod. salts	Alk.	0·5	26
10.9.33	Sod. salts	Alk.	0·1	20
11.9.33	Sod. salts	Alk.	0·2	24
12.9.33	Sod. salts	Alk.	0·3	26
13.9.33	Sod. salts	Alk.	0·5	24
14.9.33	Sod. salts	Alk.	1·0	26
15.9.33	Sod. salts	Alk.	1·0	16
16.9.33	Sod. salts	Alk.	0·4	18
17.9.33	Sod. salts	Alk.	3·0	20
18.9.33	Sod. salts	Alk.	3·0	20
20.9.33	Sod. salts	Alk.	4·8	22
21.9.33	Sod. salts	Alk.	1·7	20
22.9.33	Sod. salts	Alk.	0·9	18
23.9.33	Sod. salts	Alk.	0·6	22
24.9.33	Sod. salts	Alk.	0·8	20
25.9.33	Sod. salts	Alk.	1·0	20

Case 4

Date.	Medicine.	Reaction.	Alb.	Amount. oz.
31.8.33	Nil	Acid	5·0	18
1.9.33	Nil	Acid	5·0	26
2.9.33	Nil	Acid	4·5	16
3.9.33	Sod. salts	Slightly alk.	6·0	18
4.9.33	Sod. salts	Slightly alk.	8·0	20
5.9.33	Sod. salts	Alk.	No deposit	24
6.9.33	Sod. salts	Alk.	12·0	27
7.9.33	Sod. salts	Alk.	0·6	18
8.9.33	Sod. salts	Alk.	0·6	26
9.9.33	Sod. salts	Alk.	1·0	22
10.9.33	Sod. salts	Alk.	4·5	24
11.9.33	Sod. salts	Alk.	2·0	20
12.9.33	Sod. salts	Alk.	6·0	24
13.9.33	Sod. salts	Alk.	6·0	24
14.9.33	Sod. salts	Alk.	1·0	24
15.9.33	Sod. salts	Alk.	0·5	26
16.9.33	Sod. salts	Alk.	No deposit	22
17.9.33	Sod. salts	Alk.	4·8	16
18.9.33	Sod. salts	Alk.	3·0	20

Patient then absconded.

This table shows that on some days the albumin figure can be very low, or 'No deposit' registered, yet next day a large amount is found.   See Case 4 dated 5.9.33, 6.9.33, and 7.9.33.   We went carefully into this and ruled out the possibility of the patient having eaten other articles of food unknown to us, but we are unable to establish the definite cause for this variation.

In one patient who was attending a dental clinic eight miles away, it was noticed that his albumin percentage often rises after he has ridden this distance in an ambulance.   It was also noted that if any nephrotic case had any rise of temperature the albumin percentage in the urine increased.   We cannot explain the significance of these observations.

not present. Hyaline granular, casts, and epithelial cells were found. *Urea concentration test* : fasting 180 c.c. 1·2 per cent., the first specimen 190 c.c. 1·4 per cent., and second specimen 35 c.c. 2·2 per cent., third specimen 40 c.c. 2·5 per cent. *Blood examination* : total proteins were 4·9 grm. per cent., albumin 2·75 grm. per cent., globulin 1·62 grm. per cent., urea 29 mg. per cent., cholesterol 434 mg. per cent.

As this was one of the first cases, and we were still in the early days of the investigation, the acid treatment was continued, and on 11.4.33 the cholesterol figure was 545 mg. per cent.

Alkaline treatment was commenced on 18.4.33, and on 20.5.33 the cholesterol figure was 300 mg. per cent., finally this fell to 153 mg. per cent.

Case 6.   Chinese male, was admitted into hospital (No. 1233) on 11.3.33, aged 28 years.   On 15.6.33 he presented the typical nephrotic syndrome, i.e. swollen all over, with normal heart and blood-pressure.   Fluid was found in serous cavities.   The urea concentration was good, and urine albumin 0·5 per cent.   Casts were granular and hyaline.   Cells, epithelial only.   *Blood proteins* : the total proteins were 4·84 grm. per cent., fibrinogen 0·9 grm. per cent., albumin 2·59 grm. per cent., globulin 1·55 grm. per cent., urea 40 mg. per cent., cholesterol 416 mg. per cent., non-protein nitrogen 42 mg. per cent.   On 15.6.33 he was put on to the alkaline régime.   On 19.7.33 cholesterol was 214 mg. per cent., with no oedema, and albumin 0·25 per cent.   His general condition improved so much that the patient absconded.

Case 7.   Chinese male, admitted into hospital (No. 4848) on 20.9.33, aged 32 years.   He complained of pain and swelling of the abdomen for one and a half months, with oedema of the feet, legs, face, hands, and scrotum. He rested for a few days, and improved, but on return to work in the jungle his symptoms reappeared.   During the swollen periods he passed very little urine, which was red in colour.   He was a non-drinker, had worked eight years in the Colony as a rubber-tapper and woodcutter.   In China he was a farmer.   He had had gonorrhoea five years previously, also malaria, but was treated by the Estate Doctor with quinine and never had it again.   He had no other illness.

On admission he was pale, and well built.   There was a slight malaise, but no fever and no appetite.   His legs, feet, and abdomen were swollen. There was no enlargement of the *heart*, and no murmurs, pulse 80, regular and normal arteries.   Blood-pressure was 130/110.   Expansion of the lungs equal both sides and no tenderness.   Breath sounds and vocal resonance diminished over both bases, upper lobes clear with vesicular breathing.   His teeth were bad, and tonsils were not enlarged.   *Abdomen* : no pain, rigidity or tenderness on palpation.   Free fluid was present.   The spleen and liver were not enlarged and there was no tenderness. Central nervous system : the cranial nerves were intact and motor power good.   There was no loss of sensation, and fundi and reflexes were normal.   The *urine* was straw coloured and acid sp. gr. 1025, albumin (0·8 per cent.).   No sugar, acetone, or bile salts present.   In the deposit were granular, hyaline, and epithelial casts, a few epithelial cells, and no red blood cells.   The *sputum* was thin and watery.   No blood, no acid-fast bacilli found.   No albumin or elastic fibres present.   *Faeces* were yellow and semi-solid, no occult blood or ova.   *Kidney function test.   Urea concentration* : fasting 30 c.c. 2·53 per cent., first specimen

42 c.c. 2·45 per cent., second specimen 38 c.c. 2·54 per cent. *Blood*: Hb. 80 per cent., R.B.C. 4,900,000, W.B.C. 7,500. Differential count: polys. 72 per cent., lympho. 16 per cent. eosin. 6 per cent., monos. 6 per cent., and no abnormal red cells. No malarial parasites, and Kahn and the Wassermann reaction negative. *Blood proteins*: total proteins 6·21 grm. per cent., fibrinogen 2·96 grm. per cent., albumin 2·2 grm. per cent., globulin 1·05 grm. per cent., urea 30 mg. per cent., chlorides 842 mg. per cent., calcium 8·4 mg. per cent., cholesterol 373 mg. per cent.

Progress and treatment. During the treatment periods the progress of the patient's condition was estimated by considering three factors. (1) His weight (indicating decrease or increase of oedema). (2) Albumin percentage in the urine (Esbach's method). (3) Cholesterolaemia (Cases 7, 8, and 9).

Period 28.9.33 to 9.10.33—*Acid Régime*

Weight table.		Albumin table.		Cholesterol.	
28.9.33	138 lb.	28.9.33	0·6 %	20.9.33	373 mg.
1.10.33	142 lb.	2.10.33	0·4 %	9.10.33	385 mg.
8.10.33	146 lb.	6.10.33	0·8 %		

Clinically on 9.10.33, the oedema had increased. The scrotum was enormous.

The abdomen was very tense and he had difficulty in breathing and was very unhappy. He was then put on to the alkaline treatment.

Period 9.10.33 to 24.10.33—*Alkaline Régime*

Weight table.		Albumin table.		Cholesterol.	
11.10.33	140 lb.	11.10.33	0·4 %	23.10.33	230 mg.
14.10.33	139 lb.	16.10.33	0·4 %		
23.10.33	141 lb.	18.10.33	0·2 %		
		20.10.33	No deposit		
		24.10.33	No deposit		

On 23.10.33 there was still some ascites, scrotum normal, with slight pretibial oedema. His chest was practically clear and heart normal. His weight only decreased 5 lb. after initial diuresis.

The alkaline treatment was continued, but on 12.11.33 he was visited by relations who persuaded him to return to China with them. During the period 23.10.33 to 12.11.33, however, his condition had remained satisfactory, the oedema had practically gone (still a degree of ascites), and the albumin per cent. was still under control as this table shows:

Albumin table.

24.10.33	No deposit
25.10.33	No deposit
26.10.33	No deposit
28.10.33	0·05 %
31.10.33	No deposit
3.11.33	No deposit
7.11.33	No deposit
12.11.33	0·01 %

Unfortunately, this case, like so many of our cases, on partial recovery, insisted on discharge, and we usually then failed to keep them under observation; we can only assume that when they return to an uncontrolled diet, as experimentally proved in hospital, they again develop their primary symptoms.

Case 8. Chinese male, admitted into hospital (No. 3954) on 27.7.33, aged 26 years. He first complained of swelling of the legs and feet one month previously. Before this he had had no complaints. He noticed that the daily amount of the urine had diminished. He had been eight years in the settlement. He worked as a hawker, was married, but had no children. His diet was the ordinary coolie Chinese diet—rice, vegetables, little pork, eggs, tea, coffee, no alcohol, and no opium.

On admission he had swelling of the feet and legs, and the abdomen was slightly distended with fluid. There was no enlargement of the *heart*, rate was normal with no murmurs. Pulse 88. Blood-pressure 122/80. Breath sounds were vesicular in the upper lobes of the *lungs*, but slightly diminished at the bases of the lower lobes. There was some free fluid in the abdomen, and the liver and spleen were not palpable. The *urine* was acid, sp. gr. 1024, albumin (0·7 per cent.). No bile, sugar or acetone were found. In the deposit were granular and hyaline casts, pus, and epithelial cells. *Kidney function* : urea concentration. Fasting 2·30 per cent., first specimen 2·50 per cent., second specimen 3·07 per cent., third specimen 2·90 per cent. *Stools* contained no ova and there was no sputum. *Blood* : Hb. 75 per cent., R.B.C. 4,500,000, W.B.C. 12,500. *Blood proteins* : the total proteins were 4·92 grm. per cent., albumin 3·58 grm. per cent., globulin 1·04 grm. per cent., fibrinogen 0·3 grm. per cent., urea 21 grm. per cent., calcium 11·4 mg. per cent., chlorides 565 mg. per cent., cholesterol 214 mg. per cent.

Progress and treatment. We took this case over on 19.9.33.

Alkaline Régime—25.9.33 to 17.10.33

Weight table.		Albumin table.		Cholesterol.	
25.9.33	112 lb.	26.9.33	0·55 %	14.9.33	214 mg.
27.9.33	110 lb.	30.9.33	0·4 %	17.10.33	166 mg.
30.9.33	112 lb.	2.10.33	0·325 %		
9.10.33	110 lb.	10.10.33	0·3 %		
18.10.33	109½ lb.	13.10.33	0·3 %		
		17.10.33	No deposit		

On 17.10.33 his general condition was much better. This patient was never so oedematous as other cases on record—hence the small loss of weight. No oedema at all on 17.10.33.

Acid Régime—21.10.33 to 8.11.33

Weight table.		Albumin table.		Cholesterol.	
23.10.33	110 lb.	23.10.33	0·4 %	6.11.32	300 mg.
26.10.33	110 lb.	26.10.33	0·4 %		
1.11.33	111½ lb.	1.11.33	0·45 %		
4.11.33	111¾ lb.	2.11.33	0·7 %		
7.11.33	111 lb.	8.11.33	0·4 %		

9.11.33. Pre-tibial oedema. Slight puffiness in the face. The output of the urine was greatly diminished. On routine examination of stools ankylostoma ova were discovered. So from the period 10.11.33 to 27.11.33 the patient was put on a low milk diet and given the routine hospital treatment for ankylostomiasis. During this period no potassium salts were given, and the diet when calculated was found to be slightly on the acid side. On 5.12.33 albumin was 0·5 per cent. in urine, and on 6.12.33 alkaline régime was recommended.

Alkaline Régime—6.12.33 to 28.12.33

Albumin table.		Cholesterol.	
8.12.33	0·6 %	6.11.33	300 mg.
11.12.33	0·5 %	28.12.33	170 mg.
14.12.33	0·05 %		
20.12.33	0·05 %		
26.12.33	0·05 %		
28.12.33	0·01 %		

There was no oedema, the serous cavities were clear, and general condition good while the patient was carrying out light work.

Case 9. A Hokien male was admitted into hospital (No. 5351) on 18.10.33, aged 18 years. His occupation was that of a quartermaster. This man complained of oedema of the face, legs, scrotum, and penis for two weeks. He had no headache, giddiness, or fever, with very scanty reddish cloudy urine, no pain on micturition, appetite good with great thirst. He had no vomiting or diarrhoea. He complained of dyspnoea on slight exertion, and also palpitation and blurring of the vision. He did not remember having any other illness or similar complaint. The oedema commenced in the legs, then spread to the scrotum and abdomen. His food consisted of brown bread, Rangoon rice, canned beef, and other tinned foods while on board ship.

On examination the patient was not cyanosed, dyspnoeic, or jaundiced. Oedema of the feet, legs, scrotum, penis. Teeth fair, tonsils not enlarged. There was ascites, and the spleen and liver were not palpable. The *heart* was not enlarged, and regular with no murmurs. He had no signs of beri-beri. *Lungs*: upper lobes were clear with vesicular breathing, the bases were dull and breath sounds and vocal resonance diminished. The central nervous system was intact and fundi normal. Blood-pressure 120/90. The *urine* was alkaline 1024, albumin (0·4 per cent.). No sugar, bile, blood, or acetone was present. *Casts* were granular and hyaline. *Kidney function test*: urea concentration. Fasting 60 c.c. 2·57 per cent., first specimen 15 c.c. 2·6 per cent., second specimen 42 c.c. 2·3 per cent. Faeces showed no ova. The sputum was thin and watery, but nothing abnormal. *Blood*: Hb 60 per cent., R.B.C. 4,360,000, W.B.C. 7,400. Differential: polys. 72·7, lympho. 24·6 per cent., large monos. 2·6, eosin. nil, no malarial parasites were found. The total blood proteins were 4·31 grm. per cent., albumin 0·12 grm. per cent., globulin 3·66 grm. per cent., fibrinogen 0·57 per cent., urea 35 mg. per cent., chloride 545 mg. per cent., cholesterol 312·5 mg. per cent. Wassermann reaction and Kahn were negative.

Progress and treatment.

Acid Régime—23.10.33 to 30.10.33

Weight table.		Albumin table.		Cholesterol.	
25.10.33	128 lb.	26.10.33	0·4 %	31·10.33	300 mg.
26.10.33	130 lb.	29.10.33	0·4 %		
28.10.33	129 lb.				
30.10.33	130 lb.				

C

Alkaline Régime—31.10.33 to 14.12.33

Weight table.		Albumin table.		Cholesterol.	
30.10.33	130 lb.	31.10.33	0·4 %	27.11.33	272 mg.
6.11.33	131 lb.	4.11.33	0·6 %	14.12.33	270 mg.
7.11.33	131 lb.	10.11.33	0·025 %		
11.11.33	134 lb.	14.11.33	0·05 %		
15.11.33	136 lb.	17.11.33	0·04 %		
18.11.33	131 lb.	20.11.33	0·1 %		
19.11.33	130 lb.	23.11.33	0·05 %		
22.11.33	121 lb.	27.11.33	0·01 %		
25.11.33	118 lb.	30.11.33	0·05 %		
27.11.33	114 lb.	2.12.33	0·15 %		
1.12.33	107 lb.	5.12.33	0·2 %		
3.12.33	106 lb.	8.12.33	0·03 %		
		11.12.33	No deposit		
		13.12.33	No deposit		

Dates 7.11.33 to 15.11.33 in the weight table show clearly an observation which was noticed in many cases, namely, that on commencing the basic treatment and until the urine became alkaline, the oedema and condition of the patient became worse, but on pushing the salts the oedema rapidly decreased with the onset of a diuresis. Before the alkaline régime the urinary output in this case was as low as 6–8 oz. in twenty-four hours, whilst during it the output was over 100 oz. per twenty-four hours, and during one twenty-four hours he lost 4 lb. in weight.

Alkaline Régime—14.12.33 to 3.1.34

During this period the patient was kept on alkaline potassium salts and the basic diet. His weight remained in the neighbourhood of 107–9 lb. and he was always oedema free.

Albumin table.		Cholesterol.	
17.12.33	0·03 %	3.1.33	240 mg.
20.12.33	No deposit		
24.12.33	No deposit		
27.12.33	0·05 %		
31.12.33	No deposit		
3.1.34	0·05 %		

Case 10. Hospital No 4449—he was admitted on 27.7.32, a Hokien. Male, aged 9 years. Three years previously he commenced to swell and had pain in the abdomen. The swelling had a habit of appearing and disappearing, and on disappearing the patient suffered from fever and rigors for two to four days afterwards. He was treated with Chinese medicine (rice, and eggs soaked in urine) with good (?) but not lasting results. His diet consisted of one and a half bowls of rice and a little meat. He had no fish or vegetables. He took eggs and milk, no salt, as any salt food caused an increase of oedema.

On examination general anasarca was found, particularly in the face, abdomen, upper and lower limbs, also swelling of penis and scrotum. He had difficulty in breathing, and was very thirsty. He had no fever, but had an irritable cough, particularly at night. There was loss of appetite, and he passed very little urine. There was no cardiac enlargement, the rate and force were normal and there were no murmurs. The blood-pressure was 90/70. Breath sounds were vesicular with rhonchi, chiefly at bases. The central nervous system was normal. No changes were seen of fundi. Teeth were fair, tonsils enlarged a little, but no inflammation. The abdomen was distended

with free fluid, and the spleen and liver were not palpable. The patient had the appearance of two balls, one his head, the other his trunk, due to excessive oedema. The *urine*: sp. gr. 1010. Albumin (0·4 per cent.). No sugar or bile present. In the deposit, hyaline and epithelial casts and epithelial cells. *Kidney function*: fasting 1·11 per cent., first specimen 0·71 per cent., second specimen 2·10 per cent., third specimen 2·7 per cent. Faeces, no ova seen. *Blood*: Hb 80 per cent., R.B.C. 5,400,000, W.B.C. 11,800. Differential: polys. 22 per cent., lympho. 43 per cent., large monos. 18 per cent., eosin. 18 per cent., urea 21·6 mg. per cent., cholesterol 600 mg. per cent.

From 27.7.32 to 8.3.33 many different lines of treatment were carried out. He had high protein diet, with calcium chloride, thyroid extract, and ammonium chloride and green vegetables in large quantities, and the result of these amounted to nothing more than loss of the oedema, but persistence of albuminuria, and on several occasions relapses occurred. On 8.3.33 his condition was as follows: general condition, fair. *Heart* and *lungs*: normal. There was no ascites, but slight pre-tibial oedema. *Urine*: acid, albumin 1·8 per cent. Casts hyaline, few epithelial cells. Blood proteins, total 6·35 grm. per cent., albumin 3·39 grm. per cent., globulin 2·49 grm. per cent., fibrinogen 0·46 grm. per cent. Blood urea 20 mg. per cent., cholesterol 350 mg. per cent.

Period 8.3.33 to 30.3.33—Alkaline régime. On 30.3.33 no albumin was found in urine, even on Haller's nitric-acid test being carried out. The *urine* was alkaline, with few epithelial cells, but no casts. The alkali was stopped and a mixed diet given. Albumin reappeared in the urine on 7·4·33. The next day potassium salts were recommenced, and on 10.4.33 again the urine was albumin free. On 14.4.33 a rigid basic course of treatment was commenced and continued until 6.5.33. During this period there was never any albumin found in the urine. On 7.5.33 the potassium salts were stopped, there was no albuminuria. At this time it was thought that possibly the patient was sensitive to some particular kinds of food, and therefore, because he appeared to have had a large number of eggs in his diet, during the three years he had been ill at home, we tried out this article of food. On 9.5.33 two eggs were given and albumin was immediately found in the urine, and remained for five days. The alkaline régime was again recommenced on 15.5.33 plus two eggs each day, and a faint trace of albumin was present within six hours of eating the eggs. On 19.5.33 we fed the patient at hourly intervals with small quantities of whole egg, and had the urine tested. There was never any albumin present, and until 23.6.33 the rigid basic treatment was enforced. On 23.6.33 a mixed diet was given with eggs, and he remained free of albumin until 27.7.33. On 27.7.33 he complained of headache, coryza, and had a temperature ; albumin reappeared in the urine. For four days he was very ill, and then a typical measles rash appeared. During the febrile stage of this illness the albumin per cent. in the urine was in the neighbourhood of 0·05 per cent., but on 9.8.33 the temperature fell to normal and he became albumin free.

He was discharged from the fever hospital on 21.8.33, and readmitted under our care. On examination he was found to be free of albumin. *Kidney function test*: fasting specimen 2·4 per cent., first specimen 1·93 per cent., second specimen 2·24 per cent., third specimen 2·85 per cent. Cholesterol 175 mg. per cent. A full Chinese diet was given, and up to the day of his discharge on 16.10.33 he had had no return of his symptoms at all, and was putting on weight. This patient, however, after a few months at home subsequently relapsed again and was readmitted to hospital.

Since the completion of the investigation, but during the compilation of these notes, one or two further observations have been made, one of which at least tends to throw further light on the possible cause of nephrosis.

Dr. Shroeder of Columbia University, during the course of a world survey of the distribution of haemolytic streptococcus, visited the Clinic, and using a neucleo-protein extract of a haemolytic streptococcal culture carried out an intradermal test on eighty-five unselected cases in the wards. The test is claimed to be of diagnostic value only, and demonstrates, when positive, the fact that the patient is actually suffering, or has just recovered from an infection due to a haemolytic streptococcus. Out of the eighty-five cases tested, thirty gave a positive reaction, and amongst these thirty cases were six cases of nephrosis who happened to be in hospital at that time.

TABLE III

Serum Osmotic Pressure in Nephrotic Cases

Case No.	Date.	Albumin in grm. %.	Globulin in grm. %.	Serum osmotic pressure mg. Hg.	Oedema.
7	20.9.33	2·2	1·05	13·57	+ + +
7	23.10.33	3·19	0·06	17·62	nil
8	27.7.33	3·58	1·04	21·14	+ +
8	6.11.33	2·76	1·36	17·3	nil
9	18.10.33	0·12	3·66	5·78	+ + + +
9	14.12.33	2·05	1·24	13·00	nil

Govaert's formula : $(5·5 \times$ albumin in grm. %$) + (1·4 \times$ globulin in grm. %$)$ equals serum osmotic pressure in mg. Hg.

This observation has, in our opinion, opened up two further channels for investigation ; one, 'Is a haemolytic streptococcal infection a common causative factor in cases of nephrosis working in conjunction with a lowered resistance due to unsuitable and unbalanced diet ? ' and secondly, ' Can nephrosis be cured by first balancing and changing the diet until this semi-cured but controlled stage is reached and then immunizing the body against this infection ' ?

In a recent paper by J. B. Rennie (12) on ' Oedema in Nephritis' it is claimed that when the osmotic pressure of the serum falls below a certain level oedema appears. Using Govaert's formula, the ' critical level for oedema is a serum osmotic pressure of 14–21 mg. Hg.'

Taking Cases 7, 8, 9 and using this formula

$(5·5 \times$ albumin in grm. per cent.$) + (1·4 \times$ globulin in grm. per cent.$)$

equals the serum osmotic pressure in mg. Hg., it is seen that in all cases the serum osmotic pressure is very low both during the oedematous and the oedema-free periods. (See Table III.)

Finally, we have noticed recently that if any primary nephroso-nephritic, or a nephrotic which has passed into a nephroso-nephritic type of syndrome, is given potassium salts in large doses for a considerable period (6–8 weeks) although he remains oedema free, and has a low plasma cholesterol, he begins to complain of headache, malaise, and on investigation the only clinical
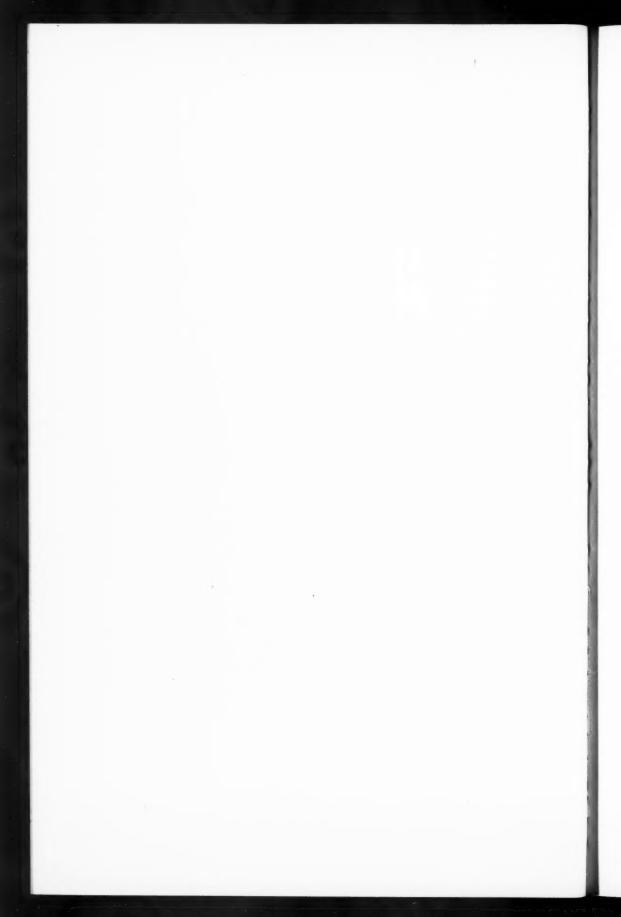
change is an alteration in the blood-pressure from normal low ranges to higher abnormal ones. The nephrotic does not appear to do this, and apparently can absorb this metal without any ill effects.

Summary and Conclusion

1. Neither ankylostomiasis nor malaria is a common factor in the aetiology of nephrosis.

2. Diet seems to be an important factor. One rich in the alkaline producing characteristics prevents an early fatal termination of the illness.

3. Potassium salts in addition to the special diet controls completely the oedema and the hypercholesterolaemia, and, partially, the albuminuria.

4. The decrease in the albumin resulting from potassium salts is not a dilution due to diuresis, but a total diminution in the output.

5. If experimentally or otherwise the alkaline régime is changed for an acid one, all the signs and symptoms of nephrosis return.

6. There is at least another undetermined factor present. The proper use of the alkaline diet plus potassium salts restrains this factor, which if allowed to proceed unchecked, often appears to cause the nephrotic syndrome to degenerate into the nephroso-nephritic or even the nephritic syndrome.

7. The results of a dermal test for a haemolytic streptococcus suggest that this organism may be a common causative factor.

REFERENCES

1. de Langen, C. D., and Eerkens, J. W., *Trans. Roy. Soc. Trop. Med. and Hyg.*, Lond., 1933, xxvii. 195.
2. Lammers, H., *Geneesk. tijdschr. v. Nederl.*, Indie Java, 1932, lxxii. 334.
3. Leiter, L., *Medicine*, Balt., 1931, x. 135.
4. Osman, A. A., *Guy's Hosp. Rep.*, Lond., 1926, lxxvi. 412.
5. Giglioli, G., *Trans. Roy. Soc. Trop. Med. and Hyg.*, Lond., 1932, xxvi. 177.
6. Surbek, K. E., *Schweiz. med. Wchnschr.*, 1932, lxii. 664.
7. Sansum, W. D., Blatherwick, N. R., Smith, F. H., *Journ. Amer. Med. Assoc.*, Chicago, 1923, lxxxi. 883.
8. McLester, J. S., *Nutrition and Diet in Health and Disease*, Philad., 1931, 2nd ed., 547.
9. Grey, E. C., *League of Nations Health Organization Report* 1928. *Food of Japan.*
10. *Chemical Analyses of Malayan Foods*, Rosedale, Aug. 1931.
11. McClendon, S. J., *Journ. Amer. Med. Assoc.*, Chicago, 1930, xciv. 1202.
12. Rennie, J. B., *Quart. Journ. Med.*, Oxford., 1933, N.S. 2, 521.

A COMPARISON OF THE PITUITARY BASOPHILIC SYN-DROME AND THE ADRENAL CORTICO-GENITAL SYNDROME [1]

By F. GRAHAM LESCHER

WITH

A REPORT ON THE PATHOLOGY
by A. H. T. ROBB-SMITH

With Plates 1 to 4

To Cushing (1) belongs the credit for first suggesting that a polyglandular syndrome, hitherto supposed to be of cortico-adrenal origin, may be due to an adenoma of the basophile cells of the anterior part of the pituitary gland.

The following are the features which he believes to be characteristic of all cases of basophile adenoma of the pituitary :

(1) A rapidly acquired and usually painful adiposity, confined to the face, neck, and trunk, the extremities being spared ; (2) a tendency to become round-shouldered, even to the point of measurable loss of height, associated with lumbo-spinal pains ; (3) a sexual dystrophy, shown by early amenor-rhoea in females and ultimate impotence in males ; (4) an alteration in nor-mal hirsuties, shown by a tendency to hypertrichosis of the face and trunk in females, as well as in pre-adolescent males, and possibly the reverse in adult males ; (5) a dusky or plethoric appearance of the skin, with purplish lineae atro-phicae ; (6) vascular hypertension ; (7) a tendency to erythraemia ; (8) variable backaches, abdominal pains, fatigability, and ultimately extreme weakness.

Less constantly present are : (1) acrocyanosis ; (2) purpura-like ecchymoses, either from bruising or occurring spontaneously ; (3) aching pains in the eyes, associated with slight exophthalmos, transient diplopia, papilloedema, dim-ness of vision, with subretinal exudate and retinal haemorrhage ; (4) extreme dryness of the skin, with pigmentation ; (5) polyphagia, polydipsia, and polyuria ; (6) oedema of the lower extremities ; (7) a susceptibility to pul-monary infections ; (8) albuminuria of slight degree, with occasional casts ; (9) a sense of suffocation and difficulty in swallowing ; (10) insomnia ; (11) polymorphonuclear leucocytosis.

In eight examples of such a syndrome, Cushing has found at autopsy that six have been associated with an adenoma of the basophile cells. In a later paper he (2) has given an account of seventeen cases coming to autopsy, including his own and others collected from the literature, twelve in women

[1] Received July 12, 1934.

and five in men.   In three the growth was large and unclassifiable; in the other eleven it was a small, circumscribed, typical basophilic adenoma.   Of the three negative cases, in two the pituitary gland was said to have been normal, but without further specification; in the third (3) no lesion was detected, even on examination of serial sections of the gland.   In addition he reports that he has three patients alive whose symptoms and signs are suggestive of this condition.   They are improving with X-ray treatment.

After reviewing his cases of hypopituitarism, Cushing (2) found two with an elevated blood-pressure.   He suggests that they also may be subjects of basophilism.

Records of similar cases are not common, but no doubt as the syndrome becomes generally known, examples will be recognized more frequently. Craig (4), at a meeting of the Association of Physicians of Great Britain and Ireland, described a typical case diagnosed during life, and on autopsy a small basophile adenoma of the pituitary gland was demonstrated.   Similar cases were mentioned at the meeting by Abraham, Davidson, Parkes-Weber, and Tidy (5).

Langdon Brown (6) has described an almost similar case, but unfortunately leave for a post-mortem examination was not obtained.   The pituitary fossa measured 17 × 7 mm.   Fuller's (7) case is one of a man who is under observation for adiposity, polycythaemia, polyuria, and hyperglycaemia, with a low metabolic rate.   Cohen (8) is at present watching the progress of three clinically characteristic cases.   Kepler (9), Pritchard (10), Lawrence (11), and Hoyle (12) have published accounts of cases clinically suggestive of Cushing's syndrome who are alive.

Before the basophilic syndrome was established, examples were described, but under other names.   Some of the cases described by Achard and Thiers (13) as instances of 'diabetes and bearded women' should probably be included in this syndrome.   So also might some conditions characterized by adiposity, osteomalacia, hypertension, and polycythaemia.   Some of the cases described under the title of 'the adreno-genital syndrome' by Charles (14) and by Broster and Gardiner Hill (15) are suggestive of Cushing's syndrome.

The present paper describes a case [2] of malignant cortical adrenal tumour, accompanied by all the cardinal, and most of the occasional, symptoms and signs of the basophilic syndrome, recently described by Cushing.

Case record.   Mrs. Ivy C., aged 35, was admitted to the Derbyshire Royal Infirmary, under the care of one of us, in October 1932, complaining chiefly of a dull pain in the chest and legs, with some shortness of breath on exertion. She had not suffered from any past illness.   One healthy child had been born fourteen years ago.   In 1929 menstruation, which had always been regular, abruptly ceased.   Her family history showed nothing of importance.

[2] An account of this case, and of the pathological findings, was communicated to the Royal Society of Medicine at the meeting on December 8, 1933 (*Proc. Roy. Soc. Med.*, 1934, xxvii. 404).

Until about 1930 she had been a slim woman, but since that time had grown stouter. Her face and body had become a dusky red, with some dryness of the skin. In 1931 she noticed that though the hair of her scalp was falling out, yet hair had started to grow on the upper lip and chin. She thought that lately she had become more hungry and thirsty than usual, and that she had passed more urine. She had also noticed that she bruised more easily. She complained of no undue weakness, and in spite of her disabilities she could do her ordinary work fairly well, nor were there any headaches or palpitations; she had no difficulty in swallowing, nor sense of suffocation. She did not complain of any subjective symptoms in her limbs, such as a creeping or burning sensation.

On examination she was a somewhat fat, plethoric, round-shouldered woman, of a striking purplish red complexion. The voice was of normal feminine pitch. Her weight was 8 st. 10 lb., and her height 5 ft. The fat was distributed over the face, neck, and trunk, the extremities having escaped, the feet and hands being quite small. There were no local tender collections of fat.

A florid cyanotic hue was especially marked on the face, forearms, legs, and upper part of the chest. On the upper and outer part of the right thigh and right arm, there were large bruises. There were no purpuric spots, nor did any appear when the venous pressure was artificially raised. The skin, especially over the legs, was dry, and in the latter situation somewhat of the texture of parchment. There was no oedema, nor pigmentation of the skin, except on the front of the abdomen and on the upper parts of the thighs, where pigmented striae were seen.

The hair on the scalp was thin, especially over the forehead. On the eyebrows it was thick. There was a coarse growth of hair on the upper lip and chin, giving a somewhat masculine but scarcely virile appearance; also round the nipples, but there was no hirsuties on the rest of the body.

There was no exophthalmos, no enlargement of the thyroid, no tremor of the hands, but the charted pulse-rate ranged between 100 and 110 when she was at rest, and was regular. The heart was enlarged, the apex beat being felt in the fifth space, $4\frac{1}{2}$ in. from the mid-sternal line. This was confirmed by a teleradiogram. An electrocardiogram showed inversion of T_1 and T_2, with left-sided preponderance. The blood-pressure was 205 mm. Hg. systolic, and 155 diastolic. This was measured on many occasions, to exclude the possibility of the condition being paroxysmal. The radial and brachial arteries were not felt to be thickened. There was no evidence of pulmonary disease.

She complained of some vague pain in the epigastrium and left renal region, but palpation of the abdomen revealed no abnormality suggestive of a suprarenal tumour; nor could the kidneys be palpated.

On examination of the neuromuscular system nothing abnormal was found, beyond that the fundi showed blurring of the disk edges, the right nasally, the left nasally and temporally. No haemorrhage into the retinae was seen. The visual fields were normal (Mr. C. H. Bamford). There was no local or general muscular weakness.

The external genital organs were normal, with normal pubic hair of feminine distribution. The uterus was subnormal in size, the cervix being atrophic. The ovaries could be palpated. The atrophic changes could be explained by post-menopausal atrophy, and there was no evidence of any change towards masculinity (Mr. N. L. Edwards).

During her stay in hospital no undue increase in her fluid intake or output

was noticed, and no abnormality in the appetite. She was a fairly cheerful, mentally alert woman, although somewhat self-conscious of the hair on the face and of her ruddy complexion. She was not drowsy, and she did not complain of headache or giddiness. Her mental outlook remained feminine.

The urine contained a trace of albumin, but no casts. Sugar was also found, but no ketonuria. The concentration for urea was: first hour 2·4 per cent., second hour 2·7 per cent. The Zondek-Ascheim test was negative, there being no indication of increased hormonic output, either as regards ovarian or anterior lobe hormones, the uterus and ovaries of the experimental animals remaining quite infantile.

The following were the results of the first examination of the blood. This was repeated on various occasions, with much the same results :

Hb	.	.	.	.	.	.	150 per cent.
R.B.C's.	.	.	.	.	.	.	6,920,000 per c.mm.
W.B.C's.	.	.	.	.	.	.	16,000 per c.mm.
Neutrophils .	.	.	.	.	.	11,840 per c.mm.
Lymphocytes	.	.	.	.	.	3,680 per c.mm.

The platelets varied between 290,000 and 110,000 per c.mm.
There were no abnormal cells.

Fasting blood-sugar	228	
1 hour after taking 50 grm. of glucose	286	All values
2 hours after taking 40 grm. of glucose	261	in mg. per 100 c.c. of
Blood urea	32–64	blood.
Serum calcium	10·1–9·6	
Serum cholesterol	148–93·7	
Serum phosphorus	2·4	

The elimination of calcium and phosphorus was briefly studied. She was given a diet containing 0·97 grm. of calcium and 1·08 grm. of phosphorus per day. After being on this diet for four days the excretions were examined for the next three days, the periods being marked off by carmine. The ashing was done according to the method of Neumann; the estimation of the calcium by that of Tisdall and Kramer; and of the phosphorus by Tisdall's calorimetric method, with the following results :

Calcium

Period. Three days.	Urine. grm.	Faeces. grm.	Total intake. grm.	Total output. grm.	Balance. grm.
	1·13	2·32	2·91	3·45	−0·54

Phosphorus

Period. Three days.	Urine. grm.	Faeces. grm.	Total intake. grm.	Total output. grm.	Balance. grm.
	1·20	1·04	3·25	2·24	+1·01

On a diet containing 100 grm. of carbohydrate, with an unrestricted amount of protein and fat, increasing doses of insulin to 20 units twice a day did not appreciably lower the blood-sugar.

The patient was examined radiographically by Mr. R. A. Laurie, who

reported that most of the bones of the trunk showed a generalized decalcification, those of the limbs having escaped.

1. The ribs on both sides showed multiple fractures, with considerable callus formation.

2. The left ischial ramus showed an old united fracture.

3. There was partial collapse of the sixth, seventh, and eighth thoracic vertebrae.

4. The pituitary fossa appeared normal.

5. The shadow in the left renal region was probably a partially calcified suprarenal tumour, which might account for the low position of the left kidney, as shown in the pyelogram, the calices in which appeared normal (Mr. G. Dyke).

The radiological appearances were not suggestive of either a generalized osteitis fibrosa or metastatic carcinoma.

In June 1933 Mr. Gerald Dyke removed a left suprarenal tumour about 6 in. in diameter. The patient's condition after operation was satisfactory for about twelve hours, when her temperature rose to 106°, and she died.

Pathological Report by A. H. T. Robb-Smith

The suprarenal tumour from the left side measured 15 × 12·5 × 5 cm. and weighed 593 grm. It was of a yellowish colour, covered by a thin capsule, through which it appeared to be breaking in two places. No remains of the normal suprarenal body could be distinguished. The cut surface showed a solid, yellowish growth, in which there were areas of haemorrhage and necrosis.

Microscopically it had the typical appearance of a cortical-cell carcinoma. It was intensely cellular, and consisted of groups of cells resembling the normal cortex, separated from one another by a fibrous reticulum bearing blood-vessels. Elsewhere the cells were arranged irregularly around thin-walled blood-vessels, and showed mitoses and abnormal nuclear formation, in places going on to giant-cell formation. No medullary cells could be seen, and the chrome reaction was negative. There was a considerable amount of fat in the tumour, both intracellularly and in the areas of cellular degeneration.

The right suprarenal gland weighed 3·4 grm. and showed no abnormality, either macro- or microscopically. With the Ponceau-Fuchsin stain, using the technique described by Broster and Vines (16), the fuchsinophile reaction was found to be positive both in the carcinoma cells of the tumour and in the cortical cells of the right suprarenal body. This reaction was negative in normal controls.

The thyroid, together with two parathyroids, weighed 17 grm. The thyroid showed normal involution; the parathyroids presented no abnormality. The pancreas weighed 19 grm. and showed marked post-mortem degeneration, but so far as could be judged was not abnormal.

The uterus and ovaries were of normal size. The latter were atrophic, and showed atresic follicles and old corpora albicantia; the blood-vessels had marked hyaline changes in the media, with obliterative endarteritis. The capsular epithelium could be made out, but all the cells were flattened. The endometrium of the uterus was narrow, and no distinction could be made between the basal layer and the superficial compact layer. The

interstitial tissue showed an increase in fibrous tissue, and a few of the glands were dilated. In fact, the genital organs had a typical post-menopausal appearance.

The bone-marrow from the middle of the shaft of the femur showed marked erythropoietic hyperplasia. The seventh and eighth ribs on the right side displayed nodular areas of marked callus formation in the sites of spontaneous fractures, but the bones as a whole were very thin and fragile. Microscopically there was an intense osteoporosis, the bony trabeculae having almost entirely disappeared, and the compact bone being extremely thin. At the fracture sites there was marked formation of callus externally, and even here the bone could be seen to be in process of absorption, particularly in the neighbourhood of vessels. The sixth, seventh, and eighth dorsal vertebrae showed much thinning and collapse, the seventh having become wedge-shaped. The same extreme osteoporotic change was seen. In neither site was the marrow hyperplasia so extensive as to suggest that the osteoporosis was due to a pressure atrophy, nor was there any fibrous replacement. In fact, the changes were those of a pure halisteresis, and identical with those obtained experimentally by Jaffe (17), in dogs which had been subjected to a slow decalcification by means of a low calcium diet and an ammonium chloride acidosis.

The pituitary body was of normal shape and weighed 0·6 grm. It was cut serially and examined by Rassmussen's (18) method. A differential cell count gave the following figures: chromophobe 31·5 per cent., acidophil 50·25 per cent., basophil 17·25 per cent. In addition, at one point a small collection of basophile cells, measuring 0·3 mm. in diameter, was found. This was not encapsulated, and had normal reticulin fibres running between the cells.

Rassmussen (19) has determined the percentage of different types of cells in the anterior pituitary in a series of normal females and given the following figures:

	Minimum.	Maximum.	Mean.
Chromophobe	32 %	74 %	49 %
Acidophil	19·2 %	57·5 %	44·2 %
Basophil	3·0 %	5·6 %	6·6 %

These show a slightly higher acidophile and lower basophile percentages than obtained in normal males. Interpreting the percentages in this case in relation to Rassmussen's findings, there is a slightly higher acidophile count, but not beyond his maximum figure, whereas the basophile figure is high above his mean and a little beyond his maximum normal. The chromophobe decrease is only to be expected, as it is well known that the chromophobe cells increase or decrease secondarily to changes in the granular cells.

As to the small collection of basophile cells which was observed, on purely pathological criteria this cannot be regarded as a true adenoma. Moreover, both Susman (20) and Roussay and Oberling (21) have found minute 'adenomata' in a large percentage of apparently normal pituitaries; and Susman goes further and suggests that the cell type found in these 'adenomata' corresponds to that cell of which there is an increase, if any, a deduction agreeing with the findings in the present case.

The Adrenal Cortico-genital Syndrome, and a Comparison with that of the Pituitary Basophilic

There is a somewhat close parallelism between the syndrome associated with a basophilic adenoma of the pituitary and the adrenal cortico-genital syndrome, which may be associated with a diffuse cortical hyperplasia or a neoplasm of the cortex of the suprarenal gland. It is not improbable that some of the cases which are said to have been due to an adrenal hyper-function have in reality the pituitary as the initial cause. In the post-mortem reports of cases of the adrenal cortico-genital syndrome few records are found of the examination of the pituitary, and fewer still include an account of the microscopical examination of serial sections of this gland.

Symptoms and signs of the adreno-genital syndrome vary according to the age of the patient, and a classification on this basis has been reviewed and discussed by Bulloch and Sequeira (22), Glynn (23), Broster and Vines (16), and others.   It is after puberty, however, that this syndrome approximates to that of the pituitary basophilic.   In a typical case, occurring in a female well after puberty, the characteristics, some of which only may be present, are : (1) adiposity, which is confined to the face, chest, abdomen, buttocks, and hips, the extremities escaping, and the figure tending to lose its feminine curve, assuming somewhat the contour of the male, though at a later stage wasting may occur ; (2) hirsuties, the pubic hair approximating to that of a male, but often being greater in amount ; (3) pigmentation and dryness of the skin, with striae atrophicae on the abdomen ; (4) cyanosis and oedema of the extremities ; (5) muscular weakness ; (6) hypertension, with cardiac hypertrophy ; (7) glycosuria and albuminuria ; (8) changes in the larynx ; (9) amenorrhoea in almost every case, with a small uterus and atrophic ovaries, and an enlarged clitoris and labia, with diminution in the size of the breasts ; (10) various psychological changes, such as the loss both of the sense of modesty and of attraction towards the male sex.   This may be very marked, as in Gordon Holmes's (24) case.   In the one reported by Langdon Brown (25) the patient was terrified because she thought she was changing into a man.

There are, however, points of difference between the two syndromes. That of the adreno-genital, occurring after puberty, is almost entirely con-fined to women.   Exceptionally in male adults there may be some slight degree of feminization, such as the female type of obesity, with well-developed breasts, and with protruding and pigmented nipples, from which there may be some secretion, accompanied by atrophy of the penis and testes, with loss of libido.   Holl (26) has reported two such cases, each suffering from tumours of the suprarenal cortex.   Parkes Weber (27) has described the condition of two men, each with a malignant cortical neo-plasm, with enlarged breasts which secreted drops of milk.   Broster and Vines (16) have given an account of four male cases associated with atrophy of the external genitalia, with high-pitched voices and a tendency towards

feminization. The basophilic syndrome, on the other hand, though occurring more commonly with women, does also occur in men.

The adreno-genital syndrome may show a fundamental difference by an attempt at sex-reversal.

The syndrome of pituitary basophilism, on the contrary, is scarcely the picture of virilism, but rather is it one of depression and inhibition.

Although the changes in appearance of patients suffering from the basophilic and adreno-genital syndromes are usually so striking, yet the glandular changes can exist without giving rise to any characteristic clinical features. Susman (20) has studied the cell structure of 250 pituitary glands obtained at routine necropsies. Twenty-three adenomatous growths of this gland, which varied in diameter from 0·2 to 0·25 mm., were found. The number of each cell type was: eight basophilic, six acidophilic, five chromophobe, and three unclassified, arising from the pars nervosa. In twenty-one glands the proportion of basophilic cells was higher than normal. Symptoms of pituitary disorder had been recognized in only two patients, and the basophilic syndrome in none.

Kepler (28) quotes Costello, who, on examination by serial sections of 1,000 hypophyses obtained at random from cases who had shown no endocrine abnormalities, found approximately 4 per cent. of basophilic adenomas.

Cases both of simple and malignant neoplasms of the adrenal cortex also occur without any of the signs of the characteristic syndrome, whilst Broster and Vines (16), in their series of cases of virilism, found several without any evidence of cortical disease.

A few cases of tumours of the adrenal cortex have been reported, with some change in the pituitary gland. The paucity of these recorded cases may be due to the lack of detailed examination of this gland. Schlüter (29) has described the case of a woman who had suffered from adiposity, amenorrhoea, and hypertension for five years, and who died of a malignant growth of the left suprarenal body, with metastases in the liver. The pituitary gland was not enlarged, but there was hyperaemia of the anterior lobe, with an increase in the eosinophilic cells, and a small decrease of the basophils. Redlich (30) has reported a cortical hypernephroma in a male, aged 18, who had suffered from polyuria, obesity, and impotence. The pituitary gland was found at autopsy to be markedly atrophic.

In Zucker's (31) case of a woman, aged 35, who had suffered from a carcinoma of the left suprarenal cortex, with virilism and polycythaemia, there was a visible enlargement of the pituitary at autopsy, but the case loses much of its value, since no microscopical examination of this gland was made. Similarly, in a case of cortical adrenal tumour, reported by Launois, Pinard, and Gallais (32), the pituitary gland was said to be normal, although no sections were examined.

Hunter (33) has reported a case of malignant cortical tumour with well-marked virilism, including polycythaemia, and decalcification of several vertebrae. In the case record there was no detailed description of the post-

mortem examination of the pituitary gland, but later Boyd (33) in a communication says: 'The case described by Hunter was in reality of adrenal and not of pituitary origin, since serial sections of the anterior pituitary disclosed no tumour.'   There is no record, however, of a differential count of the cells of the adenohypophysis.

Kepler (28) has published details of a case suggestive of Cushing's syndrome.   At operation and autopsy the adrenal glands, though enlarged and containing two small adenomas, were otherwise normal.   The pituitary gland was examined by serial sections, and contained no adenoma.

Two cases have been described by Leyton, Turnbull, and Bratton (3), and one by Kepler (34), of a tumour of the thymus with pluriglandular disturbances and signs suggestive of Cushing's syndrome.   On post-mortem examination, in addition to the thymic growths, the cortex of the suprarenal bodies was found to be greatly enlarged.   Serial sections of the pituitary showed no evidence of an adenoma, or increase in the number of the basophile cells.   The most probable explanation is that the signs and symptoms were due to stimulation of the adrenal cortex by the hyperactivity of the diseased thymus.

The following observations deal with some of the clinical conditions that are common both to the basophilic and to the adrenal cortico-genital syndromes.

Hypertension.   That there is an endocrine factor in the causation of hypertension has much in its favour.   Hypertension is a common condition in basophilism, and it was present in nine of Cushing's (2) collected cases.   He considers it reasonable to attribute this hypertension to an excess of neurohypophysial secretion, activated by a basophilic invasion.   Hypertension also occurs in 60 per cent. of acromegalic women; but in conditions where there is a diminution of secretion of the pituitary cells, such as in Simmond's disease, and also in chromophobe adenomas of the pituitary, when the posterior lobe of the gland is flattened out, the blood-pressure is generally subnormal.

Moehlig and Bates (35) have summarized an account of the work of Krause and Traube, who, after an examination of a large number of normal pituitaries, found that they contain a fairly constant number of basophile cells.   With certain diseases, such as essential hypertension, vascular sclerosis, chronic nephritis, and obesity, there is a marked increase of these cells; whereas in those suffering from diseases associated with hypotension, a diminution of this particular type of cell is found in the majority of cases. These authors believe that there is a definite parallelism between the cholesterol content of the blood and the increase of basophile cells in the pituitary.

Cushing (2) says that most of the patients with basophilic adenomas, in whom the determination has been made, show a moderate cholesteraemia. Some of these show an increase of blood calcium.   The combination is a likely factor to cause arteriosclerosis.

Carbohydrate metabolism. It has been shown both clinically and experimentally that the anterior pituitary and the adrenal cortex are intimately concerned in carbohydrate metabolism. Glycosuria is often present in acromegaly, and of the seventeen cases of basophile adenoma analysed by Cushing (2), no less than ten showed glycosuria. Conversely, in pituitary and adrenal-cortical deficiency states, produced either by disease or experimentally in animals, the tolerance for carbohydrates is increased. In hyperpituitarism, however, it has been stated by Cushing (2) that the glycosuria does not always behave as it does in diabetes mellitus, since it tends to occur in waves, and is not so amenable to treatment with insulin. The latter condition was observed in the case reported in this paper, but Lawrence (11) has described a case of Cushing's syndrome in which the glycosuria was easily controlled by diet and moderate doses of insulin.

Houssay and Biosotti (36) consider that one of the principal functions of the anterior pituitary is concerned with carbohydrate metabolism, in a sense directly opposed to the pancreatic secretion, since hypoglycaemia by fasting, or by insulin injections, is induced more easily, and tolerated less well in animals after hypophysectomy. If the pituitary is removed in a pancreatectomized dog, the signs of diabetes disappear. They conclude, therefore, that the process of endogenous sugar formation is under the control of the adenohypophysis.

The adrenal cortex is also intimately concerned with the regulation of carbohydrate metabolism. In adrenalectomized animals, Britton and Silvette (37) have found marked decrease of the blood-sugar, and also of the liver and muscle glycogen. If, however, potent adrenal cortical extract is injected, normal carbohydrate values are restored, with corresponding relief in the other symptoms of insufficiency. They have found that injections of adrenal cortical extract into normal animals increase the blood-sugar, liver, and muscle glycogen values. This is confirmed by Simmonet (38), who has found that hyperglycaemia following similar injections sets in slowly, and lasts for a prolonged time, and the return to a normal blood-value is gradual. Britton and Silvette (37) consider that the adrenal cortical secretion is primarily concerned, in conjunction with hormones of some of the other internal secretory organs, in the maintenance of normal glucose and glycogen levels of the body.

Clinically it is found that in conditions of adrenal cortical insufficiency the blood-sugar is frequently low, whereas hyperplasia and neoplasms of the adrenal cortex are often accompanied by glycosuria and hyperglycaemia.

Osteoporosis. Skeletal decalcification occurred in nine of the fourteen cases of basophilic adenoma verified by autopsy, the records of which have been collected by Cushing (2), and also in another of his cases (39). This condition is considered to be a parathyroid effect, yet in Cushing's series, although in some cases these glands were described as large and fatty (due to interlobular infiltration with fat), in only one case was an adenoma found. Even in the absence, however, of microscopic changes, it is perhaps not un-

reasonable to suppose that the parathyroid glands may be activated to produce decalcification of bone without pathological changes.

In hyperparathyroidism associated with adenomas of the parathyroid (40), a high blood calcium with a low blood phosphate, and increase of phosphatase, together with a raised calcium and decreased phosphorus elimination, should be found. But in only a few cases of pituitary basophilism has the blood chemistry been worked out. In one of Cushing's (2) cases (Miss P.) the blood calcium, phosphorus, and phosphatase were normal, with a normal elimination. In another case (Miss D.) (39) there was a negative calcium, but a positive phosphorus balance in the urine and faeces. Lawrence (11) found an increase in phosphatase in the case of basophilism which he describes. In the case described in the present paper (Mrs. I. C.), the blood calcium, phosphorus, and cholesterol were all of normal value, but during the brief period of examination there was a small increase in the output of calcium compared with the intake. A similar condition has been reported by Hoyle (12).

Rutishauser (41) has observed with osteoporotic obesity the following pituitary changes; a small basophile adenoma of the anterior lobe; numerous nodule-like basophile hypertrophies; severe malformations in the region of the posterior lobe, and increase in the number of the basophile cells of the anterior lobe; but it is not necessary for these cells to form an adenoma. The suprarenals in the case reported in this paper were either well developed or hypertrophic; in the latter both cortex and medulla were involved. The ovaries were atrophic, the parathyroids were lipomatous, and the changes in the skeleton were of an osteoporotic nature.

Osteoporosis has also been found in patients with Cushing's syndrome, although normal pituitary glands were found at autopsy. Kepler (28, 34) has reported three such cases, and Hunter (33, 42) one. The case reported in this paper is similar to these.

Summary and Conclusions

1. A case of carcinoma of the adrenal cortex is reported, which shows all the cardinal, and most of the occasional, symptoms and signs recently ascribed by Cushing to an adenoma of the basophile cells of the anterior lobe of the pituitary. A pathological examination of serial sections of the pituitary gland showed some general increase in the basophile and acidophile cells, and at one point there was a small collection of the basophile cells, 0·3 mm. in diameter.

2. In view of the case reported in this paper, and one or two others of a somewhat similar kind from the literature, it must be concluded that Cushing's syndrome, complete in its entirety, may be caused by such diseases as tumours of the adrenal cortex, and so a clinical distinction cannot always be made between these two syndromes. Every case of Cushing's syndrome

should be critically examined, including an X-ray examination of the abdomen for a shadow in the renal areas, and for the position of the kidneys.

3. Whilst it is generally accepted that the anterior lobe of the pituitary elaborates one or more gonadotropic secretions, there is no reliable evidence to show that the basophile cells are responsible for this. What evidence there is, is rather against this theory.

From the study of the basophilic syndrome, and from observations that an excess of basophilic cells occurs in such diseases as hypertension, vascular sclerosis, chronic nephritis, as well as in old age, it may be that the basophile cells are a source of some depressive inhibitory substance which can produce such conditions as a low metabolic rate, altered carbohydrate metabolism, obesity, lethargy, and lack of sex functions.

REFERENCES

1. Cushing, H., *Bull. Johns Hopkins Hosp.*, Balt., 1932, i. 137.
2. Cushing, H., *Arch. Int. Med.*, Chicago, 1933, li. 487.
3. Leyton, C., Turnbull, H., and Bratton, H. R., *Journ. Path. and Bact.*, Edinb., 1931, xxxiv. 635.
4. Craig, J., and Brennan, C., *Quart. Journ. Med.*, Oxford, 1934, N.S. iii. 57.
5. Craig, J., *ibid.*, 1933, N.S. ii. 587.
6. Brown, W. Langdon, *St. Barth. Hosp. Repts.*, Lond., 1930, lxiii. 53.
7. Fuller, C. J., *Brit. Med. Journ.*, Lond., 1934, i. 351.
8. Cohen, H., Personal communication.
9. Kepler, E. J., *Proc. Mayo Clinic*, Rochester, 1933, viii. 102.
10. Pritchard, E. A., *Proc. Roy. Soc. Med.*, Lond., 1934, xvii. 673.
11. Lawrence, R. D., *ibid.*, xxvii. 275.
12. Hoyle, C., *ibid.*, xxvii. 395.
13. Achard, C., and Thiers, S., *Bull. Acad. de méd.*, Paris, 1921, cxxxvi. 58.
14. Charles, J. R., *Bristol Med. Chir. Journ.*, 1932, xlix. 115.
15. Broster, L. R., and Gardiner Hill, J., *Brit. Journ. Surg.*, Bristol, 1932, xix. 557.
16. Broster, L. R., and Vines, A. W. C., *The Adrenal Cortex*, Lond., 1933.
17. Jaffe, H. L., *Journ. Exper. Med.*, Balt., 1932, lvi. 823.
18. Rassmussen, A. T., *Amer. Journ. Pathol.*, Boston, 1929, v. 263.
19. Rassmussen, A. T., *ibid.*, 1933, ix. 459.
20. Susman, W., *Brit. Med. Journ.*, Lond., 1933, ii. 1215.
21. Oberling, C., *Presse méd.*, Paris, 1933, xli. 1799.
22. Bulloch, W., and Sequeira, J., *Trans. Pathol. Soc.*, Lond., 1905, lvi. 189.
23. Glynn, E., *Journ. Obst. & Gynaec.*, Brit. Emp., 1921, xxviii. 23.
24. Holmes, G., *Quart. Journ. Med.*, Oxford, 1925, xliii. 143.
25. Brown, W. Langdon, *St. Barth. Hosp. Repts*, Lond., 1930, lxiii. 53.
26. Holl, B., *Deutsche Ztschr. f. Chir.*, Leipz., 1930, ccxxvi. 277.
27. Weber, F. P., *Brit. Journ. Dermat.*, Lond., 1926, xxxviii. 1.
28. Kepler, E. J., *Proc. Mayo Clinic*, Rochester, 1934, ix. 180.
29. Schlüter, A., *Frankf. Ztschr. Path.*, Munich, 1930, xl. 97.
30. Redlich, F., *Med. Klin.*, Berl., 1930, xxvi. 1255.
31. Zucker, E., *Wien. klin. Wchnschr.*, 1929, xlii. 1045.

32. Launois, F. E., Pinard, M., and Gallais, A., *Gaz. des hôp.*, Paris, 1911, lxxxiv. 649.
33. Hunter, C., Boyd, W., and Cameron, A. T., *Canad. Med. Assoc. Journ.*, Montreal, 1931, N.S. xxv. 288.
34. Kepler, E. J., Kennedy, R. L. J., Davis, A. D., Walters, W., and Wilder, R. M., *Proc. Mayo Clinic*, Rochester, 1934, ix. 169.
35. Moehlig, R. C., and Bates, G. S., *Arch. Int. Med.*, Chicago, 1933, li. 207.
36. Houssay, B. A., and Biosotti, A., *Endocrinology*, Los Angeles, 1931, xv. 511.
37. Britton, S. W., and Silvette, H., *Amer. Journ. Physiol.*, Balt., 1932, c. 701.
38. Simmonet, H., *Paris méd.*, 1932, xxii. 32.
39. Cushing, H., *Journ. Amer. Med. Assoc.*, Chicago, 1932, xcix. 281.
40. Bauer, W., Albright, F., and Aub, J. C., *Journ. Clin. Invest.*, Lancaster, 1930, viii. 229.
41. Rutishauser, E., *Journ. Amer. Med. Assoc.*, Chicago, 1933, c. 1; Abstr. *Deutsches Archiv f. klin. Med.*, Berl., 1933, clxxv. 637.
42. Cameron, A. T., *Recent Advances in Endocrinology*, Lond., 1933, 216.

FIG. 1. Mrs. Ivy C. six
years ago. Age 28

FIG. 2. Present condition
Age 35

FIG. 3. Present condition

FIG. 4. Present condition
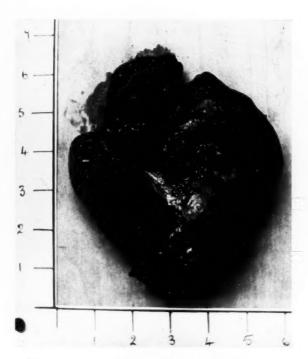
Fig. 5. Tumour of the adrenal cortex after removal
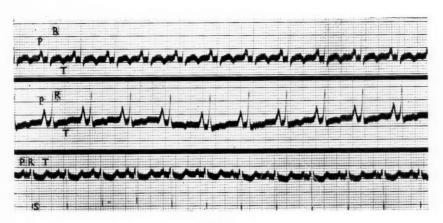
Fig. 6
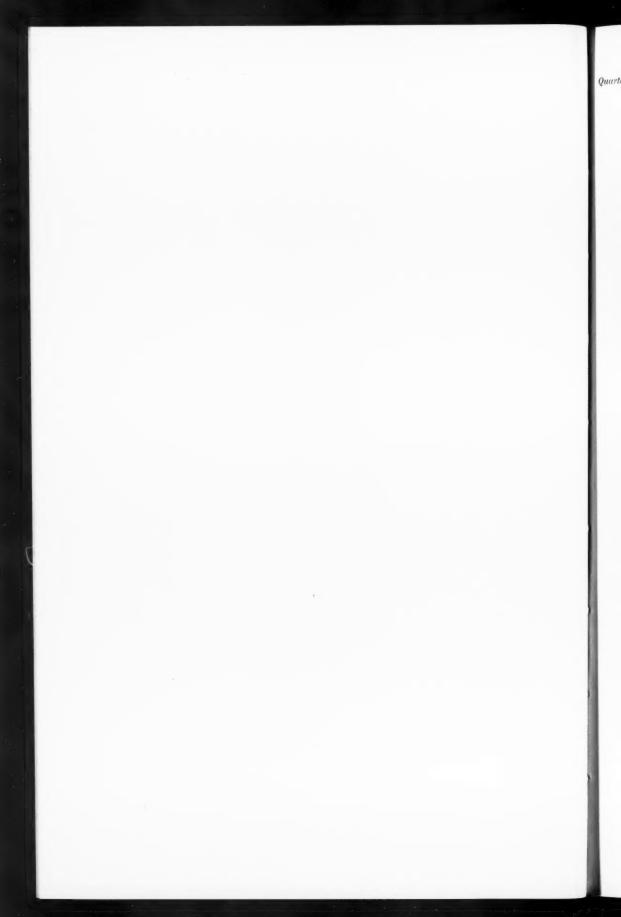
Fig. 8. Partial collapse of the 6th, 7th, and 8th dorsal vertebrae
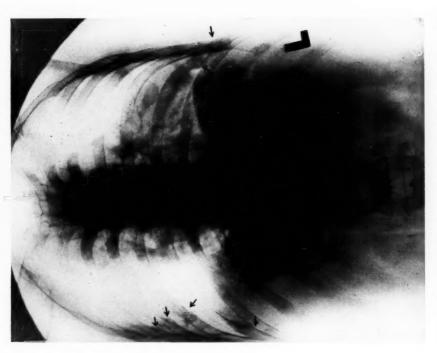
Fig. 7. Multiple fractures of the ribs on both sides and shadow in the left renal region due to a partially calcified suprarenal tumour
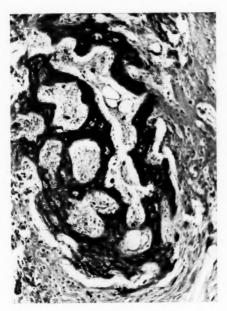
FIG. 9. A portion of rib in the region of a spontaneous fracture, showing osteoporotic changes in the new-formed callus
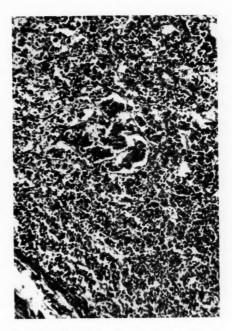
FIG. 10. Pituitary, showing the small collection of basophile cells, and the general increase of basophils. (They appear black in the photomicrograph)
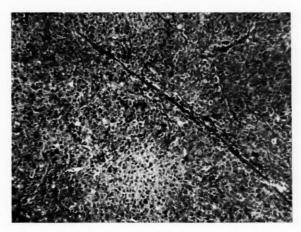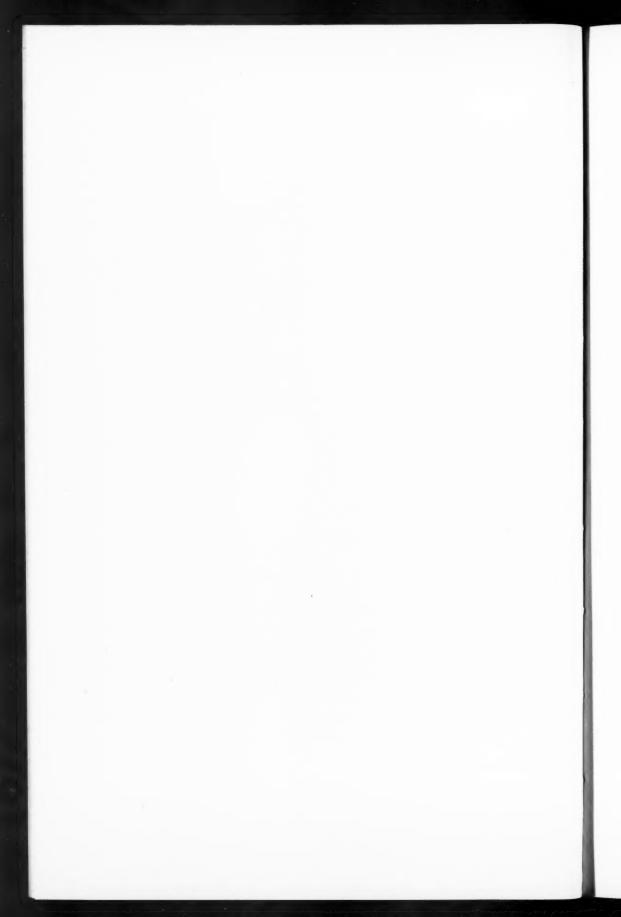
FIG. 11. Suprarenal tumour, showing the irregular cellular pattern with fine fibrous trabeculae running between the cells

SCHÜLLER-CHRISTIAN SYNDROME[1]

LIPOID-GRANULOMATOSIS WITH DEFECTS IN THE BONES, EXOPHTHALMOS, AND DIABETES INSIPIDUS

By FRANK L. HORSFALL, Jr., and W. RUSSELL SMITH

(From the Department of Medicine, McGill University Clinic, Royal Victoria Hospital, Montreal)

With Plates 5 to 7

THE clinical syndrome of defects in the bones, exophthalmos, and diabetes insipidus, which is now thought to be one rather striking, but by no means characteristic, manifestation of 'lipoid-granulomatosis', was first reported by Hand (1) in 1893. Kay (2) described the second case in 1906, and two years later Pusey and Johnstone (3) added the third. Dietrich (4) recorded the fourth case to be found in the literature, and in 1915 appeared Schüller's description (5) of two additional cases. Despite these earlier contributions, the syndrome remained relatively unknown until Christian's classical paper (6) in 1919 brought the symptom triad into full relief.

In 1928 Rowland (7) reported two cases which he believed to be of the Schüller-Christian type, and analysed twelve from the literature. Sosman (8) found a total of forty-three cases in the literature four years later, and added two of his own. In the following year Davison (9) reviewed forty-eight reported cases and added another. This year (1934) we have been able to collect fifty-nine separate cases and have added one, bringing the total now in the literature to sixty. The reader is referred to the articles by Rowland (7), Sosman (8), Davison (9), and Chester and Kugel (21) which contain excellent bibliographies and include references to fifty-three of the sixty known cases. The additional six cases that have been found in the literature are listed among our references (numbers 25 to 30 inclusive).

The following case is added to the literature because of the rarity of the syndrome, and because it happens to show almost all those changes observed in previous cases as well as a few minor abnormalities not hitherto noted. This case is additionally interesting because of the widespread distribution of the granulomatous infiltrations. It was observed clinically for a period of eight months, and a complete examination was performed *post mortem*.

[1] Received June 16, 1934.

Report of Case

J. D., male aged 4 and 4/12 years. Polydipsia, polyuria, discharging ears, changes in posture and gait, failure to grow, cutaneous nodules, defects in the bones, exophthalmos, gingivitis, loosening of the teeth.

History. The patient, a second child of French-Canadian parents, was admitted to the Royal Victoria Hospital on August 1, 1933. Birth and development throughout infancy and until the age of two years were normal. At the age of three months it was observed that he drank excessive amounts of water, and passed equally excessive volumes of urine. At two years of age the mother noticed that there was a discharge from one ear unaccompanied by pain, and followed by a similar discharge from the opposite ear. Coincidentally some twenty inflammatory lesions appeared upon the scalp. These disappeared in about three weeks. At this time he weighed 31 pounds, and this weight he has not exceeded. At three years and two months of age several small yellow papular lesions appeared on the skin of the face, abdomen, and thorax. These lesions have remained, without changing appreciably in size or shape. One month later he began holding the right shoulder somewhat higher than the left. The left shoulder later became raised, causing the neck to become shortened. Following this there occurred a gradual succession of changes in the posture and gait so that walking became difficult. There had been no headaches and no evidence of paresis. Prominence of the eyes had not been noticed by the parents. In the past two years polydipsia and polyuria have increased markedly. During the past eight months no further changes have been observed.

Because of the changes in gait and posture, and the failure in growth, he was taken to the St. Justine Hospital, Montreal, in December 1932. Roentgenograms of the skeleton were made, multiple areas of rarefaction in the skull and ribs were demonstrated and were diagnosed 'Infection métastatique'.

The family history was irrelevant. Both father and mother were alive and well. There was one sister of seven years who was normal in every respect. There was no history of a similar disease in any known relative.

Physical examination. The child was small, slightly pale, and appeared definitely less than the stated age. Both shoulders appeared elevated, the left more than the right, and the neck seemed too short. The back was rigid, particularly in the thoracic portion. The head was symmetrical and measured 49 centimetres in the occipito-frontal circumference. Scattered over it were about ten indefinite, raised, rounded, firm masses over which the scalp was freely movable. They were not tender and did not pulsate. The eyes were definitely prominent and both palpebral fissures were slightly widened. By exophthalmometer the right eye measured 11 millimetres, and the left 14. The irides were brown and the sclerae pale, bluish white. The pupils and the external ocular movements were normal. Ophthalmoscopic examination showed slight feathering of the right optic disk margin and pallor of both disks, but no papilloedema. There was moderate retinal vascular tortuosity, without venous engorgement. Both external auditory canals contained purulent discharge. There was scarring of the right drum without perforation. The left drum could not be seen, due to masses of whitish, glistening polypoid tissue blocking the external canal. The nasal passages were patent and contained no masses or polypi.

The jaw was not enlarged or prominent, the teeth were in poor condition, many were absent, and those which remained were carious, loose, and badly formed.   The gums were soft, retracted, and bled easily.   Over the dorsum of the tongue were a number of intersecting, raised, white lines forming the so-called 'geographic tongue'.   The posterior pharynx was slightly injected, and scattered over its surface were several small, white papules.   The cervical, axillary, and inguinal lymph nodes were small and discrete, slightly firm, but not tender.   The thyroid was not palpable.   The chest was normal except for a moderate outward flare to the lower costal margins. The cardiovascular system was normal, blood-pressure 80 mm. Hg systolic, and 60 mm. diastolic.   The abdomen was symmetrical and protuberant, the liver and spleen were not palpable.   The external genitalia were normal.   There was poor muscular development, but there was no limitation of joint movement except that the thoracic spine was rigid.   There were no areas of swelling or tenderness of the extremities.   The gait was waddling, swinging, and stiff-legged.   The feet were flat.   Scattered over the skin there were numerous rounded, raised, yellowish-brown papules, from 3 to 6 millimetres in diameter.   The nervous system was normal.

Laboratory examination.   Urine.   Specific gravity 1·001 to 1·004, reaction acid, no albumin, no sugar, and no acetone bodies.   No Bence Jones protein. Microscopic examination entirely negative.

Blood.   Two complete morphological blood studies were done and the figures are the averages of these.   Red-blood cells 4,590,000.   Haemoglobin 68 per cent (9·5 grm. per 100 c.c.).   Colour index 0·69.   Reticulocytes 2·0 per cent.   Fragility normal.   Corpuscular volume 31·0 per cent., mean corpuscular volume 60·3 cubic microns.   Sedimentation velocity, first hour 53 mm., second hour 63 mm.   White-blood cells 13,000.   Differential count (800 cells examined), polynuclears 36·7 per cent., rod nuclei 16·5 per cent., eosinophils 0·25 per cent., mast cells 0·25 per cent., lymphocytes 39·7 per cent., mononuclears 6·5 per cent.   Platelets 690,000.   Bleeding time and coagulation time normal.   Clot retraction normal.   Plasma refraction 55. Van den Bergh, direct delayed slightly positive, indirect less than 0·3 units of bilirubin.

Blood chemistry.   Serum calcium 9·1 mg. per cent., inorganic phosphorus 4·85 mg. per cent., sugar 91·0 mg. per cent. (a.c.), total fats 267·0 mg. per cent. (as tripalmitin), carbon dioxide combining power 37·6 vol. per cent., phosphatase 10·2 units, non-protein nitrogen 18·0 mg. per cent., cholesterol 143·5 mg. per cent., and 126·0 mg. per cent.

Blood Wassermann.   Negative.   Tuberculin (O.T.) 0·1 mg. intradermally negative.   Electrocardiogram normal.   Repeated attempts to determine the basal metabolic rate were unsuccessful.

Roentgenography.   Roentgenograms of the entire skeleton made upon two occasions showed a very striking picture, with multiple irregular defects in both the membranous and cartilaginous bones.   The most marked changes were in the skull, there being in all twenty-three defects located chiefly in the calvarium, although there were smaller defects in the bones of the base. The defects appeared as rounded or irregular, somewhat punched-out areas of rarefaction or destruction.   Both orbital plates appeared fuzzy and thickened, the left slightly more than the right.   Although the basi-sphenoid and the posterior clinoid processes appeared thickened, no defects were

found in the walls of the sella turcica on stereoscopic examination. The sella measured 8 mm. antero-posteriorly, and 8 mm. in depth. The pelvis showed the irregular areas of rarefaction occasionally noted in previous cases. This was most striking in the wings of the ilia, but numerous small, irregularly shaped defects were seen in the pubic rami and in the ischii. There were small, somewhat oval defects in several ribs. The body of the eighth thoracic vertebra was flattened and remained merely as a narrow and irregular wedge. No other vertebrae showed defects. In the mandible there was one small area of decreased density at the right angle. The left clavicle contained one round defect in its sternal third. In the left humerus there were two large irregular defects which appeared to invade the cortex. There were defects in both femora. The tibiae, fibulae, radii, and ulnae were unaffected, and there were no defects in the small bones of the hands or feet.

Biopsies of one of the cutaneous lesions from the chest, and of the larger defect in the left humerus, showed histopathological pictures identical with those found *post mortem*.

Course. The child remained in hospital for two and one-half months, and during this time his weight fell from $27\frac{1}{4}$ pounds (12·4 kilograms) to $25\frac{1}{2}$ pounds (11·6 kilograms). The temperature was normal except for occasional rises of short duration ; in one the temperature reached 103° F. Urine volume during the first month in the hospital averaged 3,661 c.c. per day, and was occasionally more than 5 litres. On one day 5,800 c.c. were excreted. The fluid intake for the same period averaged 3,737 c.c. per day, and on one day reached 5,900 c.c. Frequency of micturition was a most troublesome symptom during this entire period. Both intranasal and subcutaneous administration of 10 units of pituitrin per day were found to control the polyuria and polydipsia. By this means the urine volume was brought to normal levels.

Roentgenotherapy consisting of 300 r. units per day was given for twelve days, and the four aspects of the skull were irradiated. Although complete epilation resulted, there were no other demonstrable changes, and he was discharged unimproved.

The patient was seen at frequent intervals for the following six months, and during this time there was observed a gradual progression in many of his symptoms and signs. The weight remained constant. The appetite was extremely poor, and there was increasing pallor. In December 1933 the abdomen became markedly enlarged, contained some free fluid, and there was an associated oedema of the ankles. From time to time additional cutaneous lesions made their appearance, and in January 1934 innumerable very small skin lesions appeared, and many of these rapidly became haemorrhagic. The polyuria and polydipsia, which had been such prominent symptoms during his first admission, were partially controlled by pituitrin. Because of increasing weakness and pain on moving the legs, he was confined to bed almost constantly after January 1934.

Second admission. On April 13, 1934, the patient was readmitted to the Royal Victoria Hospital because of the sudden onset of anuria of thirteen hours' duration. In those few days immediately preceding admission there had been a marked increase in pallor, associated with the development of obvious oedema of the extremities and face, together with moderate ascites. There had also been severe constipation, with jet-black stools. The effect of pituitrin had diminished, and consequently its administration had been discontinued by the father.

Physical examination. On admission the patient was *in extremis*, breathing was rapid and laboured, pallor was extreme, and the clinical picture was entirely different from that on the previous admission. This, however, was almost entirely the result of the extreme anaemia, the oedema, and the extensive cutaneous lesions. The head had not increased in circumference, and those irregularities in the surface of the skull which had been noted previously were more indefinite. Because of the extensive oedema of the eyelids, the degree of exophthalmos was estimated with difficulty, but did not seem to be increased. The polypoid masses previously noted in the left auditory canal were unchanged, and there was no discharge from the ears. The geographic tongue and the pharyngeal papules had persisted. Several teeth had been lost, and the remainder were loose and carious. The gums were spongy and retracted. The slight lymph nodal enlargement previously noted had not increased. The chest was unchanged and the cardiovascular system was normal, except for the feeble, rapid, and running pulse. The abdomen was greatly enlarged and contained a moderate amount of free fluid. The liver and spleen were not palpable. The bladder was distended to the umbilicus. There was deep pitting oedema of the feet and legs, as well as of the hands and lower arms. The knees and hips were flexed, and active or passive motion of the legs was associated with considerable pain. The vertebral column was rigid as previously described. Scattered over the skin of the trunk, as well as of the proximal extremities, there were innumerable small, raised, yellowish and haemorrhagic lesions, many of which were surmounted by crusts. The neurological examination was normal.

Laboratory examination. The urine had a specific gravity of 1·007, very faint trace albumin, sediment contained scattered W.B.C., occasional hyaline casts, and a few nucleated cells containing small granules which were stained with Sudan III. Morphological study of the blood showed R.B.C. 750,000. Haemoglobin 13 per cent. W.B.C. 5,300. Reticulocytes 3·5 per cent. Platelets 10,000.

Fresh roentgenograms of the entire skeleton showed a marked increase in both the number and size of the bony defects, except in the skull. The latter, as a result of roentgenotherapy, displayed a striking alteration, there being a great reduction in the size and number of the defects, many of the smaller having completely disappeared, while the larger showed considerable ingrowth of new bone from the periphery. The characteristic appearance shown by the first skull plates in August 1933 had almost entirely disappeared. The pelvis showed the most striking changes of any bone, the wings of the ilia having been almost completely replaced by huge irregular defects which were surrounded by narrow frames of bone. The femora were but slightly less affected, and the marrow cavities were largely infiltrated. The defects in the left humerus had enlarged markedly, and new defects had appeared in the right humerus, while the glenoid fossa of the right scapula had almost entirely disappeared. The defects in the ribs also showed an increase in size and number.

His course in the hospital was short and progressively downward, finally terminating April 18, 1934, as a result of the extreme anaemia.

Post mortem. The body was that of a small, emaciated, male child, measuring 93 cm. in length, and weighing 11,700 grm. Significant changes were found in the skin, orbit, ears, lungs, spleen, osseous system, dura, brain, spinal cord, and pituitary.

Orbit. Firm yellowish tissue surrounded the posterior portion of the left optic nerve.

Ears. Similar firm yellowish tissue was found to fill both the middle and internal ears.

Lungs. The pleurae were smooth and glistening, and scattered over the surface of the visceral layers there were a few small, firm, yellowish nodules. The lungs were mottled pink and pale grey with slightly darker greyish areas scattered diffusely throughout.

Skull. The calvarium contained numerous partial defects and five complete perforations, the largest of which occupied the left parietal region and was 2·5 centimetres in diameter. The defects were irregular in outline, the edges had a punched-out appearance, the margins were not elevated, and on transillumination appeared more dense than the remainder of the calvarium. There were also numerous defects in the base of the skull. These occurred in both orbital plates, as well as in the middle and posterior fossae, and were filled with firm, yellowish, homogeneous material. The sella turcica contained no defects. The dura showed many flat, bright yellow plaques which on reflection appeared continuous with the tissue filling the bony defects. Over these the inner surface of the dura was in many instances smooth and glistening. In some cases the smaller bony defects were not associated with dural infiltrations. Conversely the dura surrounding the pituitary contained similar plaques, unassociated with bony change.

Vertebrae. Section of the vertebral bodies revealed a dull red marrow. In six of the thoracic and two of the lumbar vertebrae there were seen within the marrow, areas of firm, homogeneous, yellow tissue which were not sharply demarcated from the surrounding bony structure. The eighth thoracic vertebral body was flattened and compressed to a thin disk of hard bone. The adjacent intervertebral fibrocartilages were thickened, more anteriorly than posteriorly.

Ribs and sternum. The dark-reddish marrow was partially replaced by indistinct infiltrations of tissue similar to those seen in the vertebral bodies.

Femur. The marrow cavity of the left femur contained a number of large, firm, yellow masses, which occasionally compressed the adjacent cortex. These were homogeneous in appearance and could be shelled out from the surrounding bone. The remaining marrow appeared to be diffusely infiltrated by tissue similar to that seen in the vertebrae and ribs.

Brain. There was marked oedema of the brain. No other gross lesions were visible.

Cord. The cord showed no gross lesions. The dura lining the intervertebral foramina contained occasional small plaque-like collections of firm yellowish tissue.

Pituitary. No gross lesions were seen. The size, shape, and consistency were normal.

Other organs. *Heart.* The heart weighed 90 grm. The myocardium was firm and greyish red. There were no valvular defects. The aorta was smooth, white, and elastic. There were no intimal plaques. *Kidneys.* The right and left kidney each weighed 50 grm. Foetal lobulation was present: there were no gross lesions. The right ureter was slightly dilated near the

bladder. *Bladder.* Mucosa was pale grey, trabeculated, and intact. *Liver.* Weight 610 grm. The cut surface was yellowish brown, and the normal markings were poorly defined. *Stomach and intestines.* No gross abnormalities were found. *Lymph nodes.* Both the peripheral and the visceral lymph nodes were slightly enlarged and firm. *Glands.* The thyroid, parathyroids, and thymus showed no gross lesions. The pancreas was yellow, firm, and lobulated : there were no gross lesions. Adrenals not enlarged ; the cortex was of a bright yellow colour, and the medulla was thin and red. Testicles were of normal size and shape. Pineal showed no gross abnormality. The semilunar ganglion appeared normal.

Microscopic examination. Skin. The cutaneous lesions were of two rather distinct types, one representing the older papular lesions, the other the more recent and more extensive punctate eruption. The larger papular lesions were composed of closely packed masses of pleomorphic cells, which had infiltrated and replaced focal portions of the dermis and the subcutaneous tissues. Over these the epidermis was thin and attenuated. The characteristic cell type was the large, pale, oval, or round cell, with a very abundant finely vacuolated cytoplasm, and a peripheral well-stained nucleus, which was frequently eccentric. Scattered among and between these were numerous lymphocytes, plasma cells, and eosinophils, as well as occasional polymorphonuclears. There were also seen numbers of large multinucleate giant cells, in which the nuclei were chiefly peripheral and well preserved. There was a moderate amount of loose fibrous tissue and rare capillaries. Some of the lesions contained small haemorrhagic extravasations, which usually lay beneath the epidermis. Except for the presence of haemorrhages, these lesions appeared identical with those removed at biopsy.

The more recent lesions were formed by focal collections of relatively large, pale-staining cells of oval, polygonal, or fusiform shape, with large, well-stained nuclei and prominent nucleoli. Their cytoplasm was abundant and finely vacuolated, frequently producing the so-called 'foam-cell' appearance. These cells were closely packed, and were supported by a small amount of loose fibrillar tissue, in which only occasional capillaries were seen. · There was a striking deficiency in inflammatory cell infiltration as compared with the larger and older lesions, and only a rare plasma cell and lymphocyte were seen. No giant cells were found. Both within the lesions themselves and in the surrounding tissue there were frequently small patches of haemorrhage. In many instances the cellular masses appeared to arise about the various cutaneous appendages, and were quite regularly found surrounding hair follicles, or coil glands, which they compressed. The overlying epidermis was frequently invaded and replaced, and in many instances remained simply as a thin and flattened layer of homogeneous and keratinized cells. The subcutaneous tissue showed a moderate increase in normal fat. In some places the vacuolated cytoplasm took stains for fat.

Bone lesions. Numerous sections from the lesions in the ribs, vertebrae, and femur showed a remarkably constant histological picture. The myeloid tissue had been almost completely replaced and transformed as a result of the proliferation of reticular elements and the obliteration of differentiating haematopoietic cells. The lesions were composed of a dense mass of polymorphous cells and reticular elements, which appeared to compress the occasional bony spicules and the overlying cortex. The most common cell

type, exclusive of the large numbers of fibroblasts, was a large, pale-staining, oval or fusiform cell with an oval vesicular nucleus, frequently eccentric. The cytoplasm was pale and vacuolated, occasionally 'foamy' and rich in lipoid elements as shown by fat stains. Large numbers of multinucleate giant cells, also containing fat, were seen, and these occasionally had long angular processes. There were also scattered lymphocytes and plasma cells, and rare polymorphonuclears.

Dura. Sections from many areas of the dura covering the brain and the lower cord showed focal masses of large, pale-staining cells, similar to those in the skin and bone-marrow, but containing even more fat throughout their cytoplasm. Scattered between these cells were large numbers of fibroblastic cells which also contained fat. In some instances this extended throughout the length of the fibrillary processes. Small areas of hae-morrhagic extravasation were scattered throughout the lesions, which in some instances were adjacent to small blood-vessels. The cellular masses did not penetrate the dura, but occasionally invaded and replaced the superficial layers of the outer surface, and a few cells were seen infiltrating the deeper layers.

Lungs. Surrounding the smaller bronchi and arterioles there was a variably thick layer of fibroblastic tissue in which large numbers of pale-staining oval cells of large size were seen. These cells contained a granular, sometimes 'foamy', and occasionally vacuolated cytoplasm which took the fat stains. In occasional areas there were binucleate and multinucleate cells of the giant type, in the cytoplasm of which fat was found. This tissue frequently extended out into the adjacent alveolar septa which were thickened. The alveolar spaces contained numerous vacuolated macro-phages, as well as numbers of red-blood cells and leucocytes. The process in the lungs appeared diffuse, and showed no particular tendency to focal localization such as was seen in the skin and bone-marrow.

Spleen. Throughout the splenic pulp there was an irregular increase in reticular elements, and associated with this was a diffuse but scattered infiltration of large lipoid containing cells. No focal aggregations of these cells were seen, nor were giant cells found, although a few binucleate cells occurred. The lymph follicles were numerous, but were small and irregular, and appeared compressed.

Spinal cord. Sections through the cord at various levels failed to reveal any abnormalities, except in one section through the lumbar region. Here a tiny focal collection of plasma cells and lymphocytes was found in the base of the posterior horn and adjacent to a capillary. No lipoid-laden phagocytes were seen.

Brain. Detailed description of the histopathology of the brain will be reported separately.

Pituitary. There were no definite changes seen in the pars anterior. The pars posterior showed a diffuse invasion of fibrillar cells, between and among which there were numbers of large, pale-staining, oval cells. These had a finely granular cytoplasm. There were also occasional lymphocytes and plasma cells scattered throughout, but no giant cells were found.

Other organs. The heart, kidneys, liver, pancreas, adrenals, testicle, thyroid, semilunar ganglion, and mesenteric lymph node showed no ana-tomical lesions.

Lipoid chemistry. Determinations of the total lipoids and the various

lipoid fractions were made upon the liver, spleen, and the lipoid granulo-
matous lesion from the left femur (see Table I).

TABLE I

Tissue.	Weight, wet.	Total lipoid.	Fatty acids.	Phospho-lipoid.	Choles-terol.	Phospho-lipoid : cholesterol ratio.
	grm.	grm. %	grm. %	grm. %	grm. %	
Liver	2·765	4·450	1·872	1·750	0·240	7·3 : 1·0
Spleen	1·420	3·940	0·112	1·130	0·363	3·2 : 1·0
Lesion left femur	0·370	6·480	2·660	0·0	1·660	0 : 0

Relative proportions of various lipoid fractions in the liver, spleen, and bone-marrow
lesion from the left femur in a case of Schüller-Christian syndrome, expressed in terms
of the wet-weight of the tissues.

The fresh tissues were weighed and the lipoids extracted according to the
method used by Cowie and Magee (10). For the determination of the total
lipoid, an aliquot portion of the final solution was evaporated to dryness in
a tared flask and the residue weighed. Lipoid phosphorus was determined
by the method of Pregl (11), and the phospho-lipoid content calculated by
multiplying the lipoid phosphorus by the factor 26. Cholesterol was esti-
mated by the method of Myers and Wardell (12), and fatty acids were
determined by the method of Stoddard and Drury (13). All determinations
were performed in duplicate.

For the most part these results are similar to those of Epstein and
Lorenz (14), Kleinman (15), and Cowie and Magee (10), except that we
were unable to find any trace of phosphorus in the lipoid granuloma from
the femur. Our results confirm the normal lipoid and cholesterol values
for the liver and spleen as shown by Cowie and Magee. The cholesterol
content of the lesion was definitely increased, although it represented
only 25 per cent. of the total lipoid content. Previous writers have
reported the total lipoids of the lesions to consist of nearly 50 per cent.
cholesterol.

Comment

The following discussion of the Schüller-Christian syndrome is based upon
an analysis of thirty-six cases which have been reported in a complete
manner. Unfortunately it is not possible to include all the reported cases
in such an analysis because of the more or less abbreviated form of certain
reports.

Bony defects. From the records of previous cases it appears that any
bone in the skeleton, or any number of bones, may be affected by the lipoid
granulomatous process. In analysing thirty-six of the more complete
reported cases we have found the various bones to be involved as indicated
in Table II. Whereas the syndrome was first believed to affect only the
membranous bones, it seems obvious from the table that the process shows
no real predilection for any particular osseous site. The apparent frequency
with which the skull has been reported as affected, may be due partly to
the stress which has been placed upon this manifestation in earlier cases.

Roentgenograms of the bony lesions are striking, in that the latter appear to be areas of almost complete decalcification. They present a somewhat irregular, although frequently circular, outline which suggests a punched-out or trephine-like loss of substance. In the skull, if numerous lesions be present, this is sufficiently well marked to suggest Gruyère cheese. In reality the lesions are merely focal collections of lipoid granulomatous tissue which proliferate within the medullary cavity, and as they enlarge erode the cortex to a greater or less extent. Except in those cases which had been treated by roentgen-rays, as reported by Sosman (8), there has been no evidence of bone regeneration in the various defects, nor do they tend to diminish in size, but rather to enlarge insidiously.

TABLE II

Site.	Defects.	No defects.	No mention.
Skull	34	2	0
Sella	8	17	11
Pelvis	20	6	10
Long bones	17	9	10
Mandible	10	—	26
Ribs	7	—	29
Vertebrae	6	2	28
Maxilla	5	—	31
Scapulae	3	—	33

The sites of the various bone defects in thirty-six cases of Schüller-Christian syndrome.

Exophthalmos. As originally described, exophthalmos was a characteristic sign of the syndrome, and in our analysis it has been found with comparative frequency. In the thirty-six cases exophthalmos was recorded in twenty-eight, was absent in six, and was not mentioned in two. Of those with exophthalmos, the abnormality was unilateral in fourteen. Necropsies on cases having exophthalmos, in which mention has been made of the orbital contents, have shown uniformly intra-orbital xanthomata. In Wheeler's case (16) the eye was enucleated before death, and a large mass of xanthomatous tissue was found to surround the optic nerve. Frequently the prominence of the eyes makes its appearance as a unilateral phenomenon, which gradually increases in extent, and often becomes bilateral.

Diabetes insipidus. Bailey and Bremer (17) have demonstrated quite conclusively that anatomical lesions causing diabetes insipidus must lie in the region of the tuber cinereum, and that injuries to the pituitary or its stalk do not lead to the production of this abnormality in water balance. Camus and Roussy (18) have confirmed their results.

It is now known that the tuber and the tuberal region are connected with the pituitary and its stalk by definite nerve tracts, and also by a series of space-like 'channels', the exact function of which is as yet obscure. These two regions and their connexions have been collectively called the 'anterior mechanism'. While artificially or naturally produced lesions of the tuber or tuberal region lead to diabetes insipidus, the extract of the

posterior lobe is specific in controlling this dysfunction. Consequently it appears that the 'anterior mechanism' as a whole entity, rather than through its separate parts, is related to the control of water balance.

In this connexion it is of importance that in seventeen cases of Schüller-Christian disease, in which definite statements are made concerning the sella, fourteen showed no recognizable abnormality on roentgenogram, despite the existence of prominent diabetes insipidus. It may be of importance to point out that although a lateral view of the sella in our case appeared to show a sellar defect, this was not confirmed on stereoscopic examination. It is conceivable that in some, at least, of the previously reported cases, in which sellar lesions were found, stereoscopic examinations of the region might have demonstrated normal sellae.

Thompson, Keegan, and Dunn (19) examined the hypothalamic and pituitary regions in their case more carefully than have other investigators, and found lipoid granulomatous infiltrations in the region of the tuber, while the pituitary itself was unaffected. Conversely, Lichty (20) and Rowland (7) demonstrated partial lipoid granulomatous destruction of the sella in cases which did not show diabetes insipidus. Chester and Kugel (21) reported diffuse lipoid granulomatous infiltration of the posterior pituitary, similar to that found in our case, and their case also had diabetes insipidus. They make no mention, however, of the hypothalamic region.

Clinical manifestations. *Age.* The disease manifests itself typically in early childhood, as shown by the appearance of the first symptom in one-half of thirty-six cases at two years or less of age. The average age of onset in the entire group was 6·56 years, but this is abnormally raised by the inclusion of five cases who were twenty years or more of age at the onset of symptoms. The youngest case was twenty-one months, and the oldest forty years of age.

Sex. Males are more commonly affected than females, in the ratio of 3·1 : 1·0.

Race. There does not appear to be any racial predilection, nor are any races known to be immune. There is no demonstrable familial tendency.

Aetiology. Rowland (7) is credited with having made the first important contribution concerning the nature of the disease. He grouped it with other dysfunctions of lipoid metabolism and classified the condition among the 'xanthomatoses'. Epstein and Lorenz (14) showed by chemical analyses of the tissues from cases of Schüller-Christian, Niemann-Pick, and Gaucher's diseases a partial chemical specificity, as regards the predominant lipoid type, and held that the diseases were chemically distinguishable. They also were first to demonstrate that the lesions of Schüller-Christian syndrome contained relatively large amounts of cholesterol, and by fractional analysis that the lipoid content of the lesions showed a reversal of the usual phospholipoid : cholesterol ratio. Kleinman (15) confirmed these results, as also did Cowie and Magee (10). Except in the values given by Kleinman, previous authors have found no significant lipoid changes in organs not affected by

lipoid granuloma. Our results are in agreement, except that no phosphorus could be found in the femoral lipoid granuloma, and somewhat less of the total lipoid was estimated as cholesterol. Von Gierke (22) has grouped the syndrome among the so-called storage diseases, and on the chemical evidence of previous writers holds it to be the result of abnormal cholesterol storage. Recently Sobotka *et al.* (23) have demonstrated a lipolytic enzyme deficiency in the tissues from a case, and put forward the hypothesis that a failure in normal metabolism is resultant upon the decreased enzymatic content, which allows of excessive cholesterol deposition in the reticulo-endothelial system particularly. How closely these various hypotheses, formed largely from the isolated observations upon one or two cases, approach the true underlying cause of the disease must remain conjectural for the present.

Symptoms and signs. The disease manifests itself by a great variety of symptoms and signs, and of these almost any one may form the presenting symptom. As well as the very common manifestations which include defects in either the membranous or cartilaginous bones, exophthalmos of one or both eyes, and diabetes insipidus of greater or less degree, there also occur with considerable frequency the following symptoms. These we list in order of decreasing incidence; retarded growth, gingivitis, carious teeth, pain at the site of the bony lesions, and discharging ears. Slight lymph node enlargement, splenomegaly, and blue sclerae have been found in a few cases. Occasionally cutaneous or mucosal ' xanthomata ' have been described, and rarely retardation of mentality. Hypogenitalism has been seen in a very few cases, although in one instance sexual precocity has been observed.

Although it appears true that this variety of signs and symptoms is due to the variable distribution of the lipoid-granulomatous lesions, and that, as Sosman has pointed out, no one of the originally described triad (defects in the membrane bones, diabetes insipidus, and exophthalmos) is essential to the diagnosis, none the less it is peculiarly interesting that in the sixty reported cases, thirty-six have shown this full quota of the classical signs. Quite possibly this is evidence that a large number of cases of this particular type of lipoid metabolic dysfunction have gone unrecognized, or at least unreported. However, the relatively specific localization of lesions in a generalized disease, to involve areas as accurate in their position as those leading to the production of diabetes insipidus, speaks for a rather uniform regional predilection such as is seldom seen in other disease processes. Few generalized diseases can boast the production of a symptom triad as striking and as characteristic as that of defects in the membranous bones, exophthalmos, and diabetes insipidus in 60 per cent. of reported cases.

Laboratory findings. These are of no particular aid in diagnosis, there being almost no constant abnormalities of the blood either chemically or morphologically. There is frequently, however, an anaemia of greater or less extent, which may become more marked as the disease progresses, and in the late stages may become extreme. In our case and that described by

Lichty (20), the blood-findings indicate a myelophthisic anaemia, resultant upon massive bone-marrow infiltration, The white-blood count is usually normal, but there may be a leucocytosis as high as 30,000. The differential count is not characteristic, but a monocytosis occurs with relative frequency. Except in those cases with diabetes insipidus, the urine shows no abnormalities. In those instances in which the basal metabolic rate has been determined, it has been within normal limits. Blood cholesterol values have been reported in fifteen cases, and of these eleven are within normal limits. In the other four the cholesterol is moderately elevated.

Prognosis. The disease is usually slowly progressive, often terminating fatally in childhood, but sometimes continuing into adult life.

Therapy. The treatment is highly unsatisfactory, there being to date no therapeutic procedure which has materially altered the course of the disease. Sosman has demonstrated the efficacy of local roentgenotherapy, in reducing the size of the bony defects, but concurrently there has been a tendency for lesions not treated to enlarge in some cases. In our case this marked diminution in the size of the treated lesions, and the simultaneous progression of the untreated lesions was conclusively demonstrated.

Pathology. Following Rowland's contribution in 1928 (7) many investigators agreed that the process is one type of generalized 'xanthomatosis', which tends to manifest itself in lesions which arise principally in the bone-marrow. These lesions slowly proliferate and enlarge, so as to infiltrate or replace the adjacent tissues.

In 1930 Chester (24) concluded from a study of two cases that the basic lesion was a 'chronic, non-infectious, abacterial, inflammatory, granuloma due to the deposition of lipoid substances in the involved tissues'. He held that the granuloma had three main constituents; (1) the characteristic foamy lipoid cell, the specific element that contains the lipoid substances; (2) the inflammatory cellular exudate, a response of the tissue to the lipoid substances; (3) connective-tissue proliferation.

In our case these three main characteristics of the typical lesions have been found with unusual uniformity in the various tissues examined microscopically. In so far as the designation 'lipoid granulomatosis', first suggested by Chester, is consistent both with the results of chemical studies and pathological studies of the lesions in Schüller-Christian syndrome, it appears to have more justification than the non-committal term 'xanthomatosis' as suggested by Rowland. In as much as cholesterol has been found to be the predominating lipoid in the lesions in all cases in which this has been studied (Epstein and Lorenz, Kleinman, Cowie and Magee, Horsfall and Smith), it seems fitting that the more specific term 'cholesterol granulomatosis' be applied to the disease.

Summary

1. A case of Schüller-Christian syndrome is reported. The case was observed clinically during two admissions to the hospital, and finally a complete autopsy was performed.

2. Pathological studies of the tissues indicate that the lesions are granulomatous in nature and contain large quantities of lipoids. Fractional chemical analyses of the lipoids in the lesions demonstrate the predominance of cholesterol. This confirms the work of other investigators.

3. Fifty-nine other cases of Schüller-Christian syndrome have been collected from the literature. Thirty-six completely reported cases have been analysed, and it is upon the basis of this series that the disease is discussed.

4. Although 'lipoid granulomatosis', as used by Chester, is more accurate than the term 'xanthomatosis', it is suggested that the former could with more exactness be modified to 'cholesterol granulomatosis'.

REFERENCES
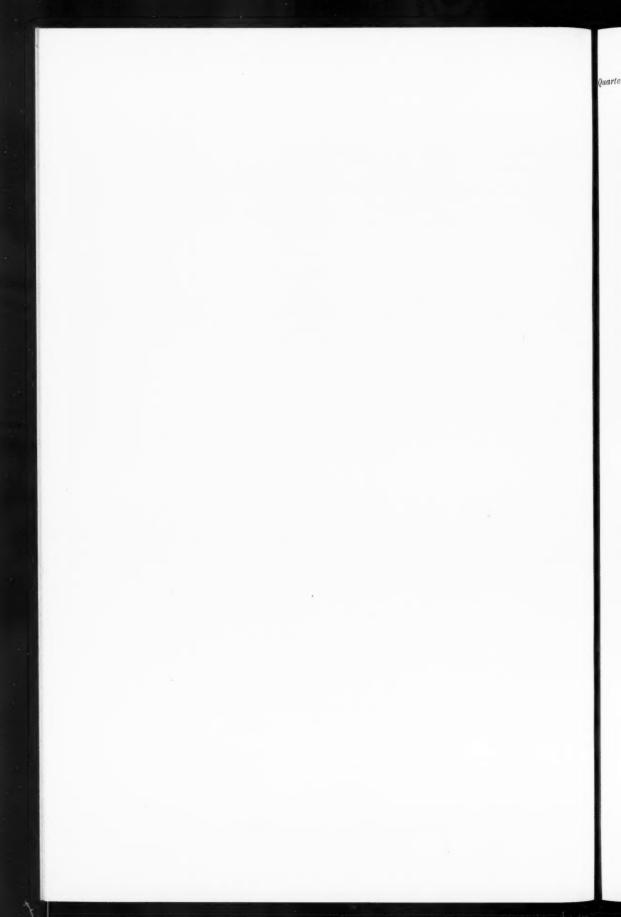
1. Hand, A., *Arch. Pediat.*, N. York, 1893, x. 673.
2. Kay, T. W., *Penn. Med. Journ.*, 1906, ix. 520.
3. Pusey, W. A., and Johnstone, O. P., *Journ. Cutan. Dis. incl. Syph.*, N. York, 1908, xxvi. 552.
4. Dietrich, A., *Virchows Arch. f. path. Anat.*, Berl., 1913, ccxii. 119.
5. Schüller, A., *Fortschr. a. d. Geb. d. Roentgenstr.*, Leipz., 1915, xxiii. 12.
6. Christian, H. A., *Med. Clin. N. Amer.*, Philad., 1919, iii. 849.
7. Rowland, R. S., *Arch. Int. Med.*, Chicago, 1928, xlii. 611.
8. Sosman, M. C., *Journ. Amer. Med. Assoc.*, Chicago, 1932, xcviii. 110.
9. Davison, C., *Arch. Neurol. and Psych.*, Chicago, 1933, xxx. 75.
10. Cowie, D., and Magee, M., *Arch. Int. Med.*, Chicago, 1934, liii. 391.
11. Pregl, F., *Die quantitative organische Microanalyse*, Berl., 1923, 2nd ed.
12. Myers, V. C., and Wardell, E. L., *Journ. Biol. Chem.*, Balt., 1918, xxxvi. 157.
13. Stoddard, J. L., and Drury, P. E., *ibid.*, 1929, lxxxiv. 741.
14. Epstein, E., and Lorenz, K., *Ztschr. f. Physiol. Chem.*, Berl., 1930, cxcii. 145.
15. Kleinman, H., *Virchows Arch. f. path. Anat.*, Berl., 1931, cclxxxii. 613.
16. Wheeler, J. M., *Arch. f. Ophth.*, Berl., 1931, v. 161.
17. Bailey, P., and Bremer, F., *Arch. Int. Med.*, Chicago, 1921, xxviii. 773.
18. Camus, J., and Roussy, G., *Journ. de physiol. et de path. gén.*, Paris, 1922, xx. 509, 535.
19. Thompson, C. Q., Keegan, J. J., and Dunn, A. D., *Arch. Int. Med.*, Chicago, 1925, xxxvi. 650.
20. Lichty, D., *ibid.*, 1934, liii. 379.
21. Chester, W., and Kugel, V. H., *Arch. Path.*, Chicago, 1932, xiv. 595.
22. Von Gierke, E., *Med. Klin.*, Berl., 1931, xxvii. 576 and 611.

23. Sobotka, H., Glick, D., Reiner, M., and Tuchman, L., *Biochem. Journ.*, Lond., 1934, xxvii. 2031.

24. Chester, W., *Virchows Arch. f. path. Anat.*, Berl., 1930, cclxxix. 561.

25. Schüller, A., and Ghiari, H., *Wien. klin. Wchnschr.*, 1930, xliii. 153.

26. Kienbock, R., and Schneck, F., *Beit. z. klin. Chir.*, Berl., 1932, clvi. 237.

27. Meworach, L., and Kienböck, R., *Roentgenpraxis*, Leipz., 1932, iv. 76.

28. Snapper, I., and Parisel, C., *Quart. Journ. Med.*, Oxford, 1933, N.S. 2, 407.

29. Dalitsch, W. W., *Ill. Med. Journ.*, 1933, xliii. 131.

30. Bilderback, J. B., Hunter, W. C., and Menne, F. R., *Northwest Med.*, Wash., 1934, xxxiii. 137.

DESCRIPTION OF PLATES

PLATE 5, FIG. 1. Photograph of patient, August 1933. The peculiar posture and the raised shoulders are well shown, as in the prominence of the left eye. The small, raised, cutaneous nodules are just visible on the face, abdomen, and forearms.

FIG. 2. Roentgenogram of the skull, August 1933. The multiple irregular defects in the bones are quite characteristic in appearance.

PLATE 6, FIG. 3. Roentgenogram of pelvis and femora, April 1934. There is a tremendous increase in the size and number of the bony defects in all the bones shown.

FIG. 4. Photograph of patient, April 1934, eight months after the first photographs were taken. There has been a tremendous increase in the number and size of the skin lesions, and a great number are haemorrhagic. Many purpuric spots, unassociated with lesions, are present but cannot be distinguished in the photograph.

PLATE 7, FIG. 5. Photomicrograph of a cutaneous lesion. The granuloma is almost entirely confined to the dermis, but is beginning to compress the overlying epidermis, and has broken through this at one point. The apex of the lesion surrounds a hair follicle.

FIG. 6. High-power magnification of Fig. 5. The granuloma is composed of large, pale-staining cells with foamy, lipoid-filled cytoplasm and vesicular nuclei. There are also many multinucleate giant cells which also contain lipoid. Scattered lymphocytes, plasma cells, and polymorphonuclears are seen.

FIG. 7. High-power magnification of lesion from the left humerus showing large, closely packed cells with lipoid-filled cytoplasm. At the periphery of the field a multinucleate giant cell is seen.

Fig. 2

Fig. 1

FIG. 4

FIG. 3

FIG. 5

FIG. 6

FIG. 7
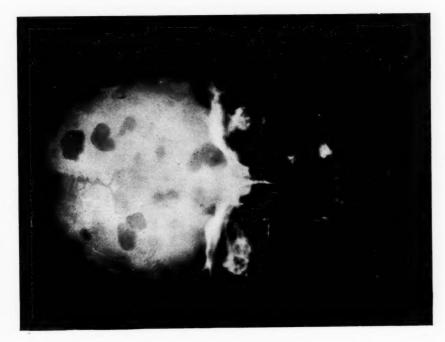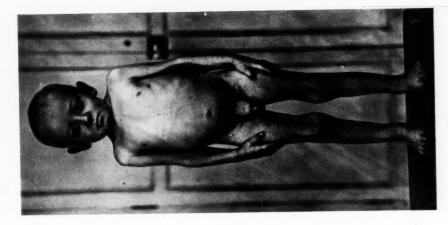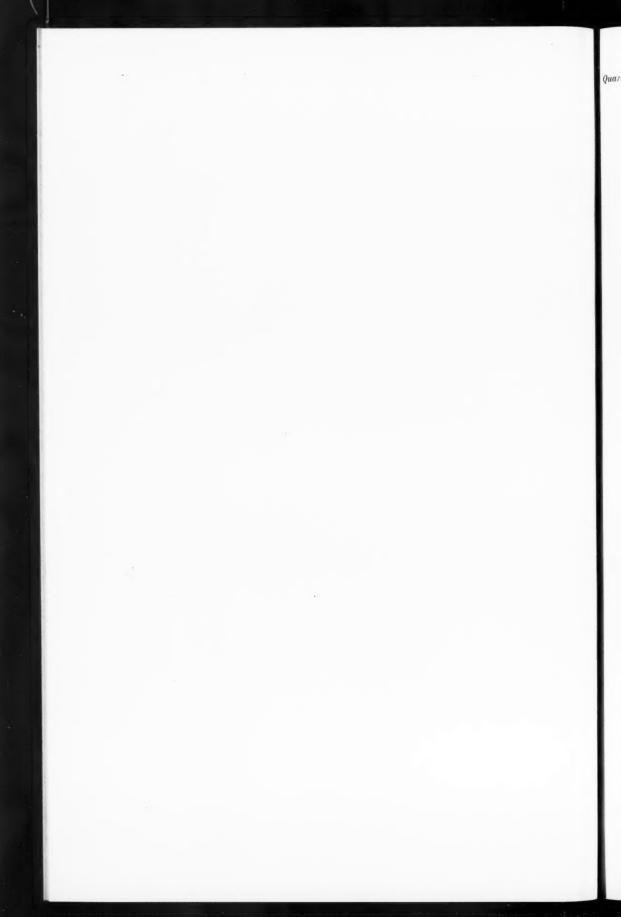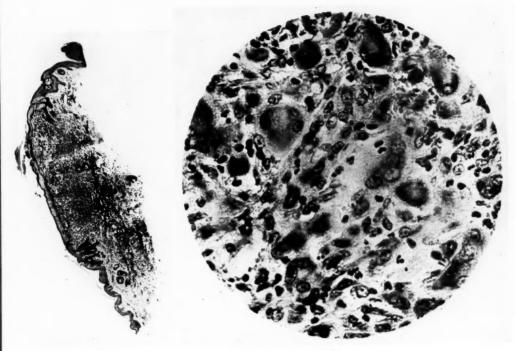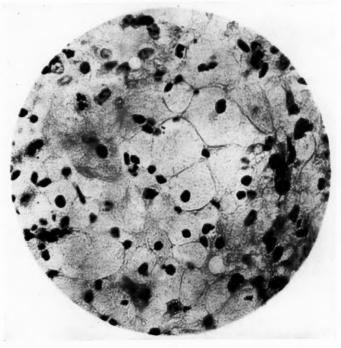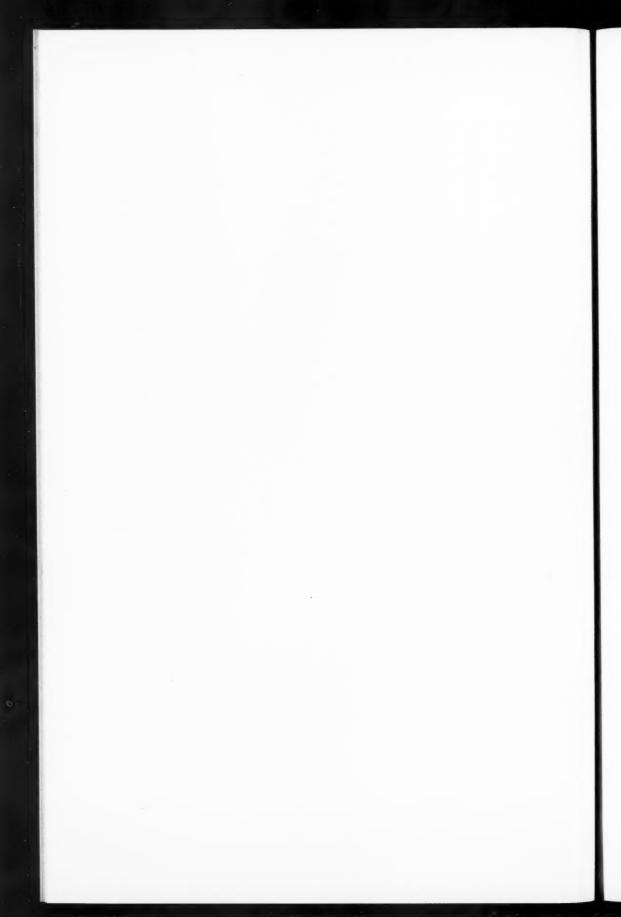
THE SECRETION OF URINE IN DIABETIC COMA [1]

By R. A. McCANCE and R. D. LAWRENCE

(From the Biochemical and Diabetic Departments, King's College
Hospital, London)

Introduction

A FORM of diabetic coma with evidence of accompanying renal failure has been recognized and reported by physicians in all countries interested in medical science. Much of the evidence presented, however, fails to exclude the possibility of the pathological phenomena being extrarenal in origin. Thus the oliguria, anuria, and raised blood urea so often recorded in diabetic coma are in themselves no proof of renal failure. Such phenomena are well recognized complications of circulatory failure and of severe dehydration when the kidney is not primarily involved. This has led some investigators to the view that such changes in diabetic coma are general rather than local in origin and that renal failure need not be invoked to explain them.

We have been interested in this subject for a number of years and have attempted to study it by making comparative examinations of the blood and urine, and controlling as far as possible those extrarenal factors likely to influence the results. Such control is not easy and may be impossible in patients dangerously ill and urgently requiring treatment, and we feel that, while new facts have been brought to light, animal experiments will be necessary to solve the problem completely.

A Consideration of Previous Work

Urinary tube-casts. Morbid anatomy. Casts and albuminuria are not more common in healthy diabetics than in other persons. Albuminuria is the rule in diabetic coma and it is often accompanied by a sudden shower of hyalo-granular casts in the urine. These are sometimes referred to as 'Kulz's' casts, although Ebstein (1881) seems to have been the first to describe them, followed by Fichtner (1888), Sandmeyer (1891), and Nebelthau (1896). They tend to disappear as soon as the coma has begun to yield to treatment and the circulation to improve. They have been observed in severe ketosis apart from fatal coma (Joslin, 1924) and are not necessarily associated with

[1] Received October 16, 1934.

functional renal failure. On the other hand, Mördre (1921) and Pelligrini (1931) have both described diabetic comas complicated by signs of renal failure but without casts. Further Blum, Grabar, and van Caulaert (1928, 1929) recorded comatose diabetics whose urines were free from casts after a few hours of treatment, but whose blood urea continued to rise for days. These casts are not of value in prognosis.

The post-mortem examination of the kidney has yielded conflicting and unsatisfactory evidence. It is evident either that the same morbid changes have been interpreted quite differently by various observers, or that the anatomical changes have no bearing on the functional disturbance. Argy (1925), Metzger (1927), Snapper (1927–28), Kraus and Seyle (1928), and Warburg (1924–25) are agreed that, naked-eye, the kidneys are large, yellow, or fatty, but most variable histological appearances have been described: mild sub-acute nephritis (Paddock (1924)); early acute glomerulo-nephritis with little change in the tubules (Löwenberg and Joel (1928)); necrosis of the tubules (Argy (1925); Dreschfeld (1886)), with, however, little polymorph infil-tration (Argy (1925); Warren (1930)); granulation, vacuolation, and swelling of the tubules (Elmer and Scheps (1928)); changes resembling those of nephrosis (Metzger (1927); Bayer (1930)); and severe changes resembling those of mercuric-chloride poisoning (Labbé and Boulin (1931 b)). On the other hand, authors who were certainly dealing with functional renal failure during or after diabetic coma, such as Appel and Cooper (1927), Coburn (1930), Weiss (1927) were unable to find any renal damage at necropsy. Chauffard and Rendu (1912) also reported a case with a terminal blood urea of 160 mg. per 100 c.c. in which so little post-mortem evidence of renal involvement was evident that they attributed the rise of blood urea entirely to dehydration.

No attempt has been made here to review all the changes described in the kidneys in diabetic coma. The classical descriptions of Armanni, Erhlich, and others have been summarized by Lepine (1909) and Warburg (1924–25). The examples given, almost all from patients with signs of functional renal failure, have been quoted merely to show how variable the post-mortem appearances have been. But it seems generally agreed that the kidneys are not of the secondary contracted type usually associated with nitrogen retention.

The excretion of water and urea. Oliguria, and even anuria, have certainly been recognized clinically as complications of diabetic coma since very early times, but Colin (1868) appears to have been the first to produce chemical evidence that the excretion of urea might fail in diabetic coma. If the oliguria or increased concentration of blood urea proceed *pari passu* with the development of coma and is the only sign which suggests a disturbance of renal function, it is difficult if not impossible to be certain that these changes are truly renal in origin and not rather due to dehydration, low blood-pressure, or the increased protein catabolism associated with intense diabetes. Blood-urea figures, ranging mostly from 60–160 mg. per 100 c.c., have frequently been reported during diabetic coma, but as all the above factors are not always considered, they scarcely require critical review.

Brunton (1924), Ambard et al. (1925), Bayer (1930), Begg (1925), Dinkin (1927), Imrie and Skinner (1924), Jungmann (1926), Kraus and Seyle (1928), Labbe and Boulin (1931 a. b.), Chauffard and Rendu (1912), Christiansen and Holst (1929), Dolore (1925), Gottschalk and Muller (1930), Hugounenq et al. (1913), McCann (1925); McCay (1919–20), Argy (1925), Chabanier et al. (1927), Coburn (1930), Mördre (1921), Payne and Poulton (1925), Rudy and Levin (1927), Ingram and Rudd (1932).

If on the other hand the urine passed is not only small in amount but of very low specific gravity in spite of a concentrated plasma, or if the blood urea continues to rise in spite of a perfectly adequate flow of urine, then there is proof, if not of failure, at any rate of a perversion of renal function. Thus Fitz (1917) showed that the 'urea index' might become progressively worse as coma developed, and McCay (1919–20) has provided another good example of this renal dysfunction.   One patient's blood contained 130 mg. per 100 c.c. of urea and the urine 1,300 mg. per 100 c.c.   Oliguria set in, and next day, not long before death, the blood contained 250 mg. of urea per 100 c.c. and the urine 300 mg. per 100 c.c.   Similar findings have been recorded by Bulger and Peters (1925) and Lorant (1929).   Aszodi (1928) showed that after cats had been depancreatized they became sleepy, with jerking movements suggestive of uraemia.   The blood urea rose rapidly and the percentage of urea in the urine fell.   The volumes of urine were well maintained so the excretion of water remained relatively unimpaired.

Sometimes the oliguria or rise of blood urea has been observed to follow the commencement of treatment.   Fitz seems to have reported the first example in 1917, but such observations have become increasingly common since the introduction of insulin.   The signs suggesting renal deficiency may or may not be obvious at first, but tend to become progressively worse for some hours or days.   In spite of this, recovery from the actual diabetic coma may at first proceed satisfactorily.   As the modern treatment of coma is directed largely to the removal not only of ketosis but of anhydraemia, and as the blood-pressure generally tends to rise once treatment has begun, dehydration and circulatory failure probably play no part in the production of post-coma oliguria, and when the flow of urine has been re-established after coma only a perversion of kidney function can explain a rising blood urea.

A number of the recorded cases have been collected in Table I in which the term 'blood urea' includes 'non-protein nitrogen', 'Reststickstoff', 'azotaemia', &c.   Root (1934) has recently reported three cases in which anuria developed after coma, but these are not included in the table as the first observation of the blood urea was only made at the height of the anuria.

In addition to these authors, Begg (1925), Imrie and Skinner (1924), Jungmann (1926), Lion (1924), Löwenberg (1928), Merklen (1926), Pelligrini (1931), and Rau (1930–31) have also described somewhat doubtful cases.

The excretion of ketones.   Since the recovery of acetone by distillation of diabetic urine by Petters in 1857 and by Kaulich (1860), acetone or ketonuria

TABLE I

Observer.	First blood urea observed. mg./100 c.c.	Highest blood urea observed. mg./100 c.c.	Day of treatment on which highest blood urea observed.	Outcome.	Remarks.
Ambard et al.	30	180	5	Death	Complicated by late pregnancy and labour. No oliguria recorded.
Bayer	28·9	72	6	Death	Complicated by pneumonia.
Bernard and Guillaumin	90	194	5	Death	Complicated by parotid abscess. Satisfactory volumes of urine till death.
Blum et al.	43	269	15	Recovery	—
	55	480	10	Recovery	—
Bowen and Beck	14	102	3	Not quoted	Figures are urea N.
	40	80	4	Not quoted	Figures are urea N.
	30	51	2	Not quoted	Figures are urea N.
Brunton	27	41·4	—	Not stated	Rise occurred in spite of generous fluid administration.
Dinkin	110	125	2	Death	B.P. 160 mm. Hg on 2nd day.
Feinblatt	30	75	2	Death	No ketones in urine.
Fitz	33	101	—	Temporary recovery, then death	B.U. fell again. Treated before insulin.
Fullerton et al.	33	230	6	Recovery	Extreme oliguria on 2nd, 3rd, 4th, and 5th days.
Graham et al.	47	100	4	Recovery	B.U. 30 on 8th day.
Ingram and Rudd	56	95	1	Death	—
	49	61	2	Recovery	—
	39	86	3	Recovery	—
John	162	255	8	Recovery	Phenol sulphonephthalein test paralleled B.U.
Joslin et al. (1927)	53	139	3	Not stated	—
	49	61	2	Not stated	—
	31	47	3	Not stated	—
	41	115	3	Recovery	Moderate oliguria.
(1933)	50	86	3	Recovery	—
Labbé and Boulin	85	150	1	Recovery	B.U. 50 on 9th day.
Lorant	40	92	2	Not stated	Excretion of uric acid and creatinine normal.
	47	85	3	Recovery	B.U. 47 on 6th day.
Lyall and Anderson	214	260	—	Death	—
	46	144	2	Recovery	—
	50	140	2	Recovery	—
	96	116	—		
Rabinowitch	35	98	5	Recovery	Diazo reaction +ve in urine when B.U. high.
Sezary et al.	63·8	94	2	Recovery	Azotaemia 21·2 on 8th day. Death later from pneumonia.
Warburg	129	270	4	Recovery	B.U. 17 mg./100 c.c. on 19th day. No striking oliguria.
Weiss	46	213	11	Death	B.P. normal.

has been found so often in diabetic coma that it has come to be regarded as one of its classical signs.   The presence of ketonuria does not of course constitute coma, but coma without ketonuria is extremely rare.   For the purposes of this paper four groups may be distinguished, two of which are important.

(*a*) Cases of unconsciousness in a diabetic due to some non-diabetic cause, e.g. a vascular stroke or a cerebral tumour (Dreschfeld (1881) von Frerichs (1884), and Lemann (1926).   The earlier authors recognized that these cases might not be true diabetic coma, but not all recent authors have been so careful.   Evans (1925).

(*b*) Cases of apparently true diabetic coma without ketones in the urine and in which ketonaemia was looked for and not found.   Rudy and Leven (1927); Begg (1925).

(*c*) Cases of true diabetic coma in which the urine contained few or no ketones but in which ketonaemia was present.   Hesse (1888), for example, described what must be regarded as a genuine case—the patient in coma, smelling strongly of acetone, but secreting urine in which traces only of acetone were found.   Argy (1925) found in one case of coma no acetone in the urine but acetone in both blood and cerebrospinal fluid ; and Rosenbloom (1915), Coburn (1930), Feinblatt (1924), and Payne and Poulton (1925) have recorded rather similar findings.   In these patients the kidneys were clearly at fault.   It is unnecessary to discuss those cases in which the urine was stated to contain no ketone bodies but in which the body fluids were not examined.   Oliver (1926), Roth (1929), Appel and Cooper (1927), Warburg (1924–5), Strothman (1928), Paddock (1924), Mördre (1921), McCaskey (1915), Revillet (1914), Chabanier et al. (1927), Graham et al. (1929).

(*d*) Cases in which simultaneous estimations of ketones in both blood and urine have been made.   Abraham and Altmann (1927), Appel and Cooper (1927), Bulow Hansen (1929), Elmer and Scheps (1928, 1930), Salomonson and Harboe (1925–6) have studied the partition of ketones between urine and blood.   Their results show that there is little parallelism between blood and urine, but that the ratio of the concentration of ketones in urine to the concentration of ketones in blood tends to fall as coma develops, that is, the excretion of ketones becomes more and more defective with advancing . coma.   It is evident from a study of their papers that the ability of the kidneys to excrete and concentrate ketones varies very much in different patients and in the same patient at different times, according to the nutrition of the kidney and other factors.   In Lorant's (1929) experience the concentration of ketones in the urine never fell below that in the blood, but a number of competent observers have been unable to demonstrate ketones in the urine when by the same method they could detect them in the blood. Unless one assumes that the ketones are being reabsorbed in the tubules, that is, are being treated as threshold bodies, no ketones can be filtering through the glomeruli in these circumstances.   This is an aspect of renal physiology and pathology that clearly requires investigation.

The excretion of sugar. It is rather curious that the excretion of this substance should have received so little attention in the terminal stages of coma. This may be, as Warburg has suggested in his historical review of coma, because the outcome was so universally fatal that interest was often lost in the patients' last hours. Until the advent of blood-analysis the occasional failure of the kidney to excrete sugar could hardly be appreciated, but one of the very earliest observations on the excretion of sugar is of real as well as historical interest in this connexion. As long ago as 1788 Cawley reported on a man aged 34, whose urine was ' a very light straw colour . . . sweet, fermentable with yeast, and two pounds, on evaporation, yielded about 5 or 6 oz. of sweet, black extract, exactly resembling that preparation of molasses made by confectioners for children. . . . Notwithstanding this progressive increase of fatal symptoms, the only apparent cause, the saccharine matter in the urine, daily decreased in proportion, and latterly two pounds yielded only an ounce and a half.' The colour of the urine changed at the end ' to one deeper and more natural '.

Bouchardat recorded a very typical case in 1845. The day before death this patient's urine contained 13·57 per cent. of sugar, but the urine passed just before death contained none at all. Foster (1878) and Domanski and Reimann (1901) reported identical observations. Had any of these authors been able to determine the sugar in the blood, the proof of renal deficiency would almost certainly have been produced.

On the subject of renal failure Warburg (1924–5), quoting from Lepine (1897), states that Born (1892) recorded a case in which ' the last samples of urine only contained 0·85 per cent. and 0·1 per cent. of sugar '. In this Warburg misquotes Lepine who stated that Born found 0·85 per cent. of sugar in the blood, but Lepine himself had also grossly misquoted Born who did not estimate the blood-sugar and gave the urinary findings as sugar 8·5 per cent., protein 0·1 per cent. Lepine's own case had a blood-sugar of 1·06 per cent. and the anatomical evidence *post mortem* led the author to suggest that failure of the kidneys to excrete sugar had been partly responsible for the extreme height of the blood-sugar. From a study of six cases of coma Fitz (1917) concluded that ' 5 patients showed a glycaemia which seemed proportionately higher than the corresponding glycosuria '. Joslin commented on the low percentage of sugar which might be found in the urine in coma. McCay, working in India in 1919–20, made some very pertinent observations on the excretion of sugar in coma. Making blood and urine comparisons at twenty-four hourly intervals he found in one case that in the twenty-four hours before death the blood-sugar remained practically constant at 0·55 per cent. while the sugar in the urine decreased from 2·5 per cent. to nil. This was by no means an isolated observation, and Salomonson and Harboe (1925–6) have also found that in late coma sugar may disappear from the urine in spite of persistently high blood-sugar. von Noorden (1912) wrote ' Doch muss bemerkt werden, dass manchmal im Koma der Harn . . . Zuckerfrei wird '. It has been suggested several times

since Lepine that the very high blood-sugar figures sometimes encountered terminally (Argy, 1925) are due to failure of the kidney to remove the excess from the blood.   There is no doubt that the concentration of sugar by the kidney may become much less efficient in severe diabetic toxaemia (Bulger and Peters, 1925) and recover quickly under the influence of insulin but, as with the excretion of acetone bodies, it appears that the excretion of sugar may cease entirely before the excretion of water ceases.

Epstein and Baehr found that after pancreatectomy in cats the volume of urine remained high for the next four days.   The percentage of sugar in the urine fell steadily until death, although the blood-sugar became higher. The albumin in the urine also steadily increased.   The whole syndrome therefore can probably be produced in animals under controlled conditions.

'Retention' of sugar may also be met with in the post-coma type of renal failure discussed in the previous section dealing with the excretion of urea.   Failure to excrete sugar after insulin control has been established has naturally only been rarely observed, but Blum et al. (1929) have mentioned a patient who, during the post-coma retention phase, excreted no sugar with a blood-sugar of 0·4 per cent. but later passed sugar with blood-sugar of 0·2 per cent.   Joslin has pointed out the difficulties that arise in treating such a case.

A number of authors, e.g. Warburg, have recorded sugar in the urine in coma, but no acetone bodies.   The evidence therefore, such as it is, suggests that the excretion of the latter tends to fail first, and this was also Epstein and Baehr's experience in their experiments with cats.

The excretion of ammonia and titratable acids.   In chronic nephritis with nitrogen retention there is sound evidence that the excretion of ammonia ultimately fails.   Marischler (1901), Palmer and Henderson (1915), van Slyke et al. (1925–6), Magnus-Levy and Siebert (1928).   The last authors concluded that 'Die unfahigkeit der Niere, genugende Mengen Ammoniak zu liefern, ist eine der schwersten Funktionsstörungen der Nephritis'.

On the other hand there is very little exact knowledge available about the excretion of ammonia or acid in diabetic coma.   There is evidence that there is little relation between the degree of ketonuria and the amount of ammonia excreted.   This has been variously interpreted.   Starr and Fitz (1924) suggested that other organic acids were being excreted, and Elmer and Scheps (1928, 1930) that a low excretion of ammonia coupled with a high ketone excretion was a sign of nephritis.   Wolpe (1886) noted that with the onset of coma the percentage of ammonia in the urine tended to fall, whereas that of aceto-acetic acid rose.   Rumpf (1895) recorded a case in which the percentage excretion of ammonia remained unchanged until death, although the percentage of sugar fell greatly.   Mördre (1921) found normal ammonia/acid ratios in a case of coma with pronounced nitrogen retention. Warburg's (1924–5) data, although incomplete, suggest the same thing.   As will be seen later, our present findings are in complete accord with this.

Present Investigation

Methods. Determinations in urine have been made by the following methods:

Total nitrogen	Kjeldahl (McCance and Shipp (1933)).
Urea	(*a*) Hypobromite method (Harrison (1930)).
	(*b*) Marshall's urease method (Hawk (1923)).
Ammonia	A micro-form of Folin's method of aeration at room temperature into standard acid (Hawk (1923)).
Uric acid	Folin and Wu (Beaumont and Dodds (1926)).
Creatinine	Folin (Hawk (1923))
Chlorides	Volhard's principle; the urine was heated at 100° C. with HNO_3 and excess $AgNO_3$ (McCance and Shipp (1933)).
Metallic radicles	McCance and Shipp (1933).
Titratable acidity	Titration with N/10 alkali to the phenolphthalein end point.

The following methods have been employed for blood and the accepted normals are given:

	Normal	
Urea	15–45 mg. per 100 c.c.	Archer and Robb (1925).
Serum proteins	6·5–7·5 per cent.	Kjeldahl (McCance and Watchorn (1931)).
Alkali reserve	55–75 vols. per cent.	Van Slyke gasometric (Harrison (1930)).
Plasma chlorides	340–380 mg. per 100 c.c.	Volhard's principle (Van Slyke (1923–4) and McCance and Shipp (1933)).
Creatinine	1–2 mg. per 100 c.c.	Meyers (1924) and Folin Wu (Beaumont and Dodds (1926)).
Uric acid	2–4 mg. per 100 c.c.	Folin and Wu (Beaumont and Dodds (1926) and Harrison (1930)).
Serum sodium	325–330 mg. per 100 c.c.	(McCance and Shipp (1933)). The removal of phosphates was sometimes omitted and a less micro form of the method employed.

Material. Fifteen diabetic cases, of whom thirteen were in coma, have been investigated; three of these have exhibited post-coma nitrogen retention in high degree; ten have shown nitrogen retention during coma. Some of these have died without reduction of the retention, others have lost the retention as treatment developed. In one, nitrogen retention increased slightly for the first twelve hours of treatment. The remaining two dia-

betics have not been in coma, but have exhibited similar signs of renal disorder.   The salient facts about all the cases may be found in Table II.

<div align="center">TABLE II</div>

<div align="center">*List of Cases in Present Paper*</div>

No. of Case.	Sex.	Age.	Cause of coma.	Course of the disease.
1	F	13	Digestive upset	Renal failure followed coma. Recovery.
2	M	48	Omitted insulin	Renal failure followed coma and was complicated by gas gangrene. Recovery.
3	F	54	Omitted insulin	Renal failure followed coma. Recovery.
4	F	53	Omitted insulin	Death in coma. B.U. 132. (Patient's normal = 45 mg. per 100 c.c.)
5	M	79	Untreated	Death in coma. B.U. 200 mg. per 100 c.c.
6	F	16	Omission of insulin	Death in coma.
7	M	14½	Omission of insulin	Rapid recovery after some hours' anuria. B.U. 118 on admission.
8	F	30	Omission of insulin	Death in coma. Complete anuria from admission.
9	M	—	Untreated	Death in coma. B.S. 1.53 %. B.U. 153 mg. per 100 c.c.
10	M	77	Untreated	Death in coma. B.U. 121 mg. per 100 c.c.
11	F	52	Untreated	Death in coma. B.U. on admission 120 mg., later 156 mg. per 100 c.c.
12	F	60	Gave up insulin	Died of heart failure.
13	F	20	Omission of insulin	B.U. 67 mg. on admission ; 87 mg. 12 hours later. Clinical improvement appeared uninterrupted from the time of admission.
14	M	62	—	No coma. Died 3 days after excision of rectum.
15	M	62	—	Streptococcal septicaemia. Died.

<div align="center">*Results*</div>

Most of the important earlier observations have been confirmed on one or more of our patients.   Where no new observations have been made these are mentioned very briefly.

The appearance of the urine.   Albumin and casts.   In our experience the appearance is rather characteristic and has been too much ignored by previous authors.   Even in the presence of many signs of renal failure, such as a rising blood urea, the urine is usually highly pigmented, often turbid, and looks concentrated.   Its volume may remain normal, or so slightly decreased as to excite no suspicion of what is happening or to suggest the need for further investigation.   It is interesting to recall Cawley's (1788) description of the altered appearance of the urine with deepening coma. The signs of functional renal failure may come on with or without obvious oliguria.   We have always observed oliguria in the severe post-coma type (Cases 1, 2, 3) but not necessarily in the others, and notably not in the non-comatose cases.   Large numbers of casts have been found on admission in only one of the cases of coma here recorded (Case 7) and he made a rapid recovery.   On the other hand, innumerable casts were found in the urines during the post-coma phase of oliguria.   These were of the short

FIG. 1.

Day of observation	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Blood Pressure mg.Hg.	80/60	98/72	95/70			94/75	95/75	100/78			118/75				118/80	95/75
Serum Protein %	5·4									5·9						
Alkali Reserve vols.%	33	33	26		28			35		40			45			
Plasma Chlorides as Cl. mg./100ccs.	310	319	307		319		328			337						368
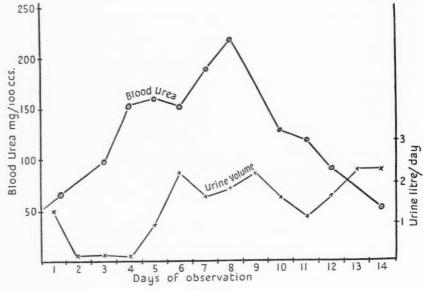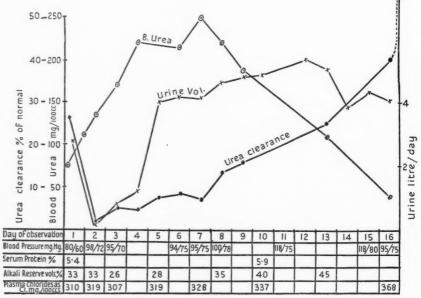
FIG. 2.

hyalo-granular type familiar in the German literature as ' Kulz zylindern '. These casts disappeared as soon as the flow of urine was re-established and before the blood urea began to fall.   It would seem that these casts should no longer be regarded as peculiar to the *onset* of coma.   They appear to be part of the renal disorder which may not become obvious until the state of coma has been relieved by treatment.

The excretion of water and urea.   All gradations of water excretion at the beginning of treatment have been observed, from polyuria to anuria, but, owing to the relative commonness of oliguria at this stage and the frequent and complicating coincidence of dehydration and low blood-pressure, only the post-coma type will be considered.   Fig. 1 shows the volume of urine excreted and the blood urea of Case 1, from soon after admission until recovery was well established.   The intake of fluid was of the order of 2,000 c.c. per day throughout.   The points to which we wish to draw attention are : (1) the period of oliguria ; (2) the subsequent re-establishment of the flow, during which time the blood urea continued to rise ; (3) the rise of the blood urea for eight days and its subsequent fall.

The patient ultimately made a complete recovery of kidney function and shortly before discharge McLean's urea concentration test gave the following result :

> 1 hour after 10 gr. urea   .   .   2·72 per cent. urea in urine
> by mouth :
> 2 hours after   .   .   .   .   2·85   ,,   ,,
> 3   ,, ...   2·95   ,,   ,,

Fig. 2 shows blood urea, urine volume, and urea clearance, alkali reserve, and plasma chlorides, blood-pressure, and serum proteins, in Case 2.   The urine volumes show that the oliguric period was relatively brief and followed by a diuresis which lasted for a week.   This last was brought about by a correspondingly high fluid intake.   On the seventh day the blood urea was still on the up-grade in spite of a diuresis of 4,000 c.c. per day for three days.   The figures for plasma proteins show that anhydraemia will not explain the oliguria ; the blood-pressure chart shows that it was not due to a temporary circulatory collapse.   It would seem, therefore, that it must have been renal in origin.   The urea clearance has been calculated from the twenty-four hour volumes and, although not of a high degree of accuracy, shows the general trend quite clearly.   Little improvement in the clearance is shown before the blood urea begins to fall.   Before discharge this patient's blood urea was 31 mg. per 100 c.c. and three hours after 15 gr. of urea by mouth the urine contained 2·54 per cent. urea.

Table III shows results from Case 3.   They differ from Case 2 in certain respects.   Thus (*a*) the oliguric period was longer and lasted several days ; (*b*) the blood urea did not rise quite so high ; (*c*) there was no diuresis, and consequently one of the signs of improvement was the rising concentration of urea in the urine.   As in Case 2 the records of the blood-pressure and the

plasma proteins show that neither circulatory collapse nor anhydraemia was responsible for the oliguria.

The rising blood ureas in all these cases, in spite of a copious flow of urine, and the low urea clearances show that the kidney was grossly disorganized as regards urea excretion.

TABLE III (Case 3)

Day of observation.	Blood-pressure mm. Hg.	Plasma proteins g. %.	Volume urine c.c.	Blood urea mg./100 c.c.	Urea clearance % of standard or max. normal.	Alkali reserve vols. %.	Plasma chlorides as Cl. mg./100 c.c.	Serum sodium as Na. mg./100 c.c.
1	80/50	7·0	460*	80	18·0	—	—	304
2	96/65	6·5	300	110	3·9	28·4	438	317
3	95/65	5·8	140	130	2·6	24·8	420	318
4	92/68	—	430†	160	—	—	—	—
5	103/79	—	720	168	5·0	31·0	370	308
7	90/65	5·95	1100†	200	8·6‡	30·3	352	297
9	—	—	1300†	156	14·5‡	26·5	349	302
11	82/58	5·85	1100†	79	34·5‡	31·0	352	302
13	75/50	—	1150	57	58·0	39·0	362	
14	80/60	—	—	39	83·0	50·0	352	

* Only covered a period of 12 hours.   † Incomplete.
‡ Calculated on 12-hour instead of 24-hour volumes.

Fig. 3 shows observations made on Case 13 which differed in important respects from Cases 1, 2, and 3. In the first place the blood-pressure was extremely abnormal for a girl of 20. It had been about 200/110 for the whole six months before admission in coma. In spite of this her renal function had been absolutely normal. In the second place coma was less deep on admission, the renal disorganization was much less severe and was all over in forty-eight hours. There was *no* oliguria. It will be observed that there was an intense diuresis on admission which passed off under treatment, but that the urine volumes did not fall below 1 c.c. per minute till thirty-six hours later, by which time recovery was well established. This case shows very clearly what Cases 2 and 3 suggested, i.e. that for the hour after admission the urea clearance may be quite good, in this case very good. In the ninety minutes following admission, Case 13 excreted 1·95 gm. of N., equivalent to 31·3 gm. of N. in the twenty-four hours—an excretion corresponding to the catabolism of 195 gm. of protein a day—and yet the blood urea was rising! During the recovery phase the blood urea began to fall and was normal before the urea clearance rose to its initial figure. This suggests very strongly that deficient excretion was not the cause of the high blood urea observed on admission. Excessive production of urea therefore probably played a part in the initial rise, and the evidence suggests that this production of urea must have been going on at a very high rate.

Defective excretion of sugar and the ketone bodies during and after coma. A failure to excrete sugar has been observed at levels known to be above

that patient's usual renal threshold.   In case No. 1, for example, this had previously been determined as being about 0·14 per cent.   During the post-coma oliguric period the urine contained only traces of sugar when the blood-sugar was known to be at least 0·246 per cent.   The two patients who were not in diabetic coma have both shown similar sugar retention.   Case 14 was in hospital under observation for some days before an operation.   During

Hours after admission	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64
Blood Pressure mm.Hg	210/110					179/112						190/115				
Serum Protein %	6·8					7·1						5·6				
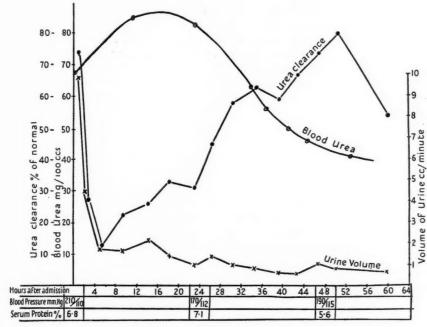
Fig. 3.

this time he was dieted but required no insulin and his urine constantly contained small but variable amounts of sugar.   At 12 noon his blood-sugar was 0·120 per cent.   Two days after the operation, excision of rectum, this patient, with a blood-sugar of 0·555 per cent., was excreting no sugar in his urine, and later with a blood-sugar of 0·66 per cent. (compare Epstein et al. 1916).   We have less exact information about Case 15, probably of the same type.   His normal threshold had never been determined but, when his blood urea was rising 50 mg. per 100 c.c. per day, he was found to be excreting no sugar when his blood-sugar was 0·350 per cent. and above.

Ketonaemia without ketonuria has been observed on several occasions. Thus a positive Rothera's test was obtained on the blood-serum but not in the corresponding urine (a) in Case 1 after coma, (b) in Case 14 who was not in coma.   In Case 10, during coma, traces only by Rothera's test were found in the urine when the reaction could be demonstrated on a drop of serum.

The excretion of creatinine.   Very few observations have been made on the

retention or excretion of creatinine, which is regrettable owing to its impor-
tance in Rehberg's work (1926) on the physiology of the kidney. This is all
the more unfortunate since it seems to be generally agreed (Peters and Van
Slyke (1931), p. 460) that most of the extrarenal factors that affect blood
urea and non-protein nitrogen influence creatinine very little. Thus in
obstruction of the alimentary tract and dehydration due to infantile diar-
rhoea, &c., the creatinine often remains normal even when the non-protein
nitrogen and urea have risen considerably. John (1925) noted that the
blood-creatinine of his comatose patient was 3·1 mg. per 100 c.c. Feinblatt
(1924) recorded a blood-creatinine of 3·3 mg. per 100 c.c. In the twelve
hours before death the blood urea rose to twice its initial figure while the
creatinine fell slightly to 3 mg. per 100 c.c. One of Root's (1934) cases had
a blood-creatinine of 5·45 mg. per 100 c.c. during the anuria which followed
coma. This fell to 1·6 mg. per 100 c.c. on recovery. In our limited
experience renal disorganization has been accompanied by a retention of
creatinine which has tended to run parallel with that of the urea.

TABLE IV (Cases 2, 3, and 13)

	Case 3.		Case 2.		Case 13.	
Day of observa-tion.	Blood creatinine mg./100 c.c.	Creatinine clearance c.c./min.	Blood creatinine mg./100 c.c.	Creatinine clearance c.c./min.	Blood creatinine mg./100 c.c.	Creatinine clearance c.c./min.
1	—	—	3·76	16·5	2·4	47·0*
2	3·86	18·4	4·16	3·0	1·6	35·0
3	4·75	6·3	—	—	1·1	60·0
5	5·2	3·5	—	—	—	—
7	6·25	5·9	—	—	—	—
8	—	—	4·35	17·2*	—	—
9	5·2	8·0	—	—	—	—
10	—	—	3·03	30·4*	—	—
11	3·3	—	—	—	—	—
13	—	—	2·38	—	—	—
14	2·6	18·5	—	—	—	—
16	2·1	22·0	—	—	—	—

* Max. clearance, i.e. minute volume > 2 c.c.

Table IV shows our results, which are to be compared with Figs. 2 and 3
and Table III. With the exception of the fourteenth and sixteenth days of
treatment (Case 3) the creatinine clearances in c.c. per minute were always
higher than those of urea, but the general resemblance is clear and it is
probable that were the creatinine data more complete the likeness might be
even closer.

The excretion of uric acid. Very few previous observations have been
made. John (1935) reported a blood uric acid of 5·2 mg. per 100 c.c. on the
day of admission which had fallen to 1·3 mg. per 100 c.c. some weeks later.
Feinblatt (1924) found 1·8 mg. uric acid per 100 c.c. in his patient on
admission and 2·4 mg. per 100 c.c. in the cerebrospinal fluid at death. We
have so far only been able to make complete observations on one case. On
admission the blood uric acid of Case 13 was 15·1 mg. per 100 c.c., twenty-

four hours later it was still 14·7 mg. per 100 c.c., but by the forty-eighth hour it had fallen to 3·6 and the clearance had risen from 9·4 to 20 c.c. per minute.

The excretion of H ions. In our experience, even when the oliguria was at its worst the urine has been very acid (Lepine, 1909). This was not due to the excretion of ketone bodies. Thus Case 2 had on admission in coma a urine of pH 4·8 (B.D.H. Capillator method). The pH was only once above 5 during the next nine days and once was as low as 4·6. In Case 3 the urine was never quite so acid and was only below pH 5 on one day. In these post-coma urines there were no ketone bodies, or at most only traces. There is evidence, too, that even during coma one may find very acid urines containing no ketone bodies if renal failure of the type under discussion has set in. Thus Case 5 had on admission a urine of pH 4·8. This was maintained till his death eight hours later, and yet the urine never contained more than traces of ketone bodies by Rothera's test. The urines of the non-comatose Case 14 were also extremely acid, pH below 5. Here, therefore, we have examples of this very acid urine in non-comatose, comatose, and post-comatose renal failure with nitrogen retention.

In Case 2, for thirty-six hours at least, the excretion of water was very deficient; for seven days the blood urea was rising; yet throughout this time the pH of the urine remained about 4·9 while the pH of the blood must have been over 7 to be compatible with life. Although, therefore, the concentration of urea in the urine was only 3 to 6 times that of the blood, the concentration of H ions in the urine was at least 100 times that in the blood. In this respect, therefore, the kidney was functioning quite normally.

The excretion of ammonia and titratable acids. Since it is now generally agreed that the kidney itself produces the excreted ammonia (Nash and Benedict, 1921; Peters and Van Slyke, 1931 &c.) and since NH_3 retention in the blood is unknown, a comparison of blood and urinary ammonia cannot be applied as a test of renal activity. Two other methods of study, however, are available, and together they provide a fairly reliable guide to the kidneys' ability to produce ammonia both during and after coma.

First, the ability of the kidney to conserve fixed base by converting acids which reach it as Na and K salts into NH_3 salts can be studied by the urinary ratio ammonia/ammonia + titratable acidity. And, secondly, the ammonia coefficient $\left(\dfrac{NH_3}{Total\ N} \times 100\right)$ is recognized as an important indication of reaction to acidosis. This is normally 2–5, but becomes much higher in acidosis.

If the ability of the kidney to excrete ammonia were to remain unimpaired during the renal disorganization under discussion the following observations might be expected.

1. The ammonia/ammonia + titratable acidity ratio would remain constant throughout gross fluctuations in the excretion of 'total' acid and in spite of other signs of renal disorganization. By 'total' acid in this connexion is

meant the total acid radicles not combined with fixed base, i.e. the titratable
acidity + ammonia.   Fig. 4 shows graphically how constant the percentage
of the 'total' acids linked to ammonia remained throughout the whole
time Case 3 was under observation.   Other data on this case showing the
failure and recovery of urea excretion during this period may be found in
Table III.   Table V shows the same phenomenon in Case 2.   It will be

Days of observation

FIG. 4.
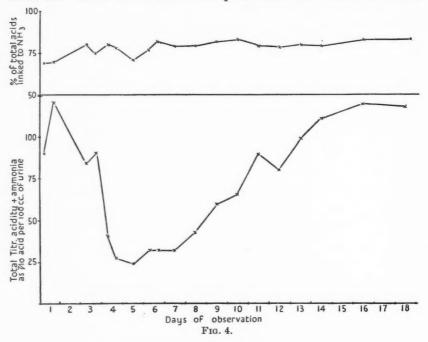
TABLE V (Case 2)

Excretion of Acid and NH$_3$

Day of observation :	1	2	3	4	5	6	7	8	9	10
Urine, volume	1395	86	920	1286	3924	3124	2532	4550	4920	6000
Titratable acidity + ammonia per day (as c.c. N/10 acid)	1660	30	212	223	660	540	465	790	1270	1200
NH$_3$ × 100/NH$_3$ + tit. acid	69	71	57	55	59	55	57	66	66	68
Total N. per day: grm.	6·1	0·24	3.0	4·1	8·7	9·7	8·3	15·5	16·4	17·0
NH$_3$ coefficient	28	13	6·3	4·7	6·3	4·2	4·5	7·0	7·2	5·1

seen that in spite of enormous variations in urinary volume and the daily
excretion of acid, the percentage linked to ammonia remained very con-
stant.   In both these cases the ammonia/ammonia + titratable acidity ratio
is rather a high one, probably owing to the shortage of fixed base in these
individuals (Gamble, Ross, and Tisdall (1923)) and the prolonged acidosis.
Fitz and Van Slyke (1917) showed that their ten normals excreted 54 per

cent. of their total urinary acids as the ammonium salts, and that thirteen untreated diabetics excreted 64 per cent. so combined. Table VI shows figures obtained in a non-comatose case (No. 14). The urea clearances show the extent of the kidneys' disorganization at the time. In spite of this, nearly half the 'total' acid excreted was linked to ammonia. This may be taken as a normal figure, for there is no reason to suppose that this case was short of fixed base. Similar results from Case 12 are shown in Table VII.

TABLE VI (Case 14)

Date.	Sept. 13.	Sept. 14.	Sept. 15.
Blood urea (mg. per 100 c.c.)	131	190	Death
Urea clearance (percentage of standard)	4·5	6·0	—
Urine pH	4·8	4·7	—
Percentage of 'total' acid as ammonia	43·0	43·0	—
'Ammonia coefficient', i.e. percentage of total N. excreted as NH₃ N.	23·0	8·3	—

TABLE VII (Case 12)

Hours after admission:	0	0–4	4–8	8–16	16–20	20–24	24–28
Ammonia coefficient	7·2	6·2	6·8	6·3	11·5	8·5	—
Percentage of total urinary acid as NH₃	65·0	49·0	63·0	70·0	85·0	86·0	Death
Urea clearance (percentage of maximum or standard normal)	—	13·0	19·0	13·0	34·0	36·0	—

TABLE VIII (Case 13)

Hours after admission:	0–1½	4–7	7–11	20–25	36–40
Ammonia coefficient	15·7	20·0	12·7	14·4	15·7
Percentage of total urinary acid as NH₃	50·0	67·0	87·0	90·0	93·0
Urea clearance (percentage of maximum or standard normal)	74·0	12·0	22·0	31·0	59·0

In considering the percentage of 'total' acid linked to ammonia one must consider both the nature of the acid being excreted and the amount of fixed base available. The kidney can probably excrete a percentage of the relatively weak ketonic acids as such without calling on base, and early in coma fixed base may be relatively easily available (Gamble, Ross, and Tisdall, 1925). One would therefore expect the highest ratios to be found, not at this stage, but later, i.e. during treatment, when, as will be described presently, these cases are excreting large amounts of hydrochloric acid. This strong acid *must* be excreted linked to base. At all events the highest ammonia ratios encountered by us have been met with during recovery (Table VIII). Table VII also illustrates this.

2. High ammonia coefficients should be encountered so long as there is a call upon the kidney to excrete acid and conserve base, and very high co-efficients might be expected if the failure to excrete urea and creatinine is not associated with a simultaneous failure to form ammonia. Further, the coefficient might be expected to show little relationship to the total nitrogen

excreted and none whatever to the urea clearance. All these expecta-
tions have been realized by our observations. Coefficients of 6–20 have
been the rule, Tables VI, VII, and VIII, and some remarkably high ones
have been obtained, e.g. 23 and 28 in Cases 14 and 2 respectively (Tables
VI and V) and higher ones even than these were encountered in Case 3.
The complete independence of the coefficient and the urea clearance may
also be seen by simultaneous study of Table V and Fig. 2 (Case 2). One
particular example may be quoted. With a total nitrogen excretion of only
0·24 gm. on the second day of observation and a urea clearance of 1·7 per
cent. of normal, the ammonia coefficient was 13 and the percentage of total
acids linked to ammonia was 71. On the tenth day, with a total nitrogen
excretion of 17 gm. in the twenty-four hours and a clearance of 19 per cent.,
the coefficient was only 5, but the percentage of the total acids in the urine
linked to ammonia was unchanged at 68. Case 13, Table VIII, illustrates
this point equally well.

It would seem that with these acute renal disorganizations, even if the
nitrogen retention is very severe, the kidney does not lose its power to form
and excrete ammonia. In acute uranium nephritis, however, the reverse
seems to be the case (Brull and Roersch, 1934).

The excretion of sodium and chloride. The excretion of chlorides in severe
diabetic toxaemia is generally recognized to be very low (Bulger and Peters,
1925), Fullerton et al. (1932) and this is our experience. The plasma
chlorides have been stated to be invariably reduced (Kuhn and Witcher
(1931)) but this is not always so (Atchley and Benedict (1930–31) and Peters
et al. (1933)) and we have found them either low or very high, *vide infra.*
There is thus a complete dissociation between the level of plasma chlorides
and the urinary chlorides, which Fullerton et al. (1932) have taken to indi-
cate renal failure. The importance of sodium has not been fully appre-
ciated and we have studied it as well as the chlorides.

TABLE IX (Case 7)

Urine.		Hours after admission.	
	0	4–24	24–31
Na m. eq./litre.	4·4	21·0	9·0
Cl ,, ,, ,,	6·0	77·0	100·0
NH$_3$,, ,, ,,	21·0	40·0	90·0

Before treatment, whatever the absolute levels of serum sodium and
plasma chlorides, the urine was generally found to contain more sodium
than chloride. Thus the urine of Case 12 contained 21 m. eq. of sodium
per litre against 7 m. eq. of chlorine. The serum sodium at the time
was 295 mg. per 100 c.c. (normal, 325–30 mg. per 100 c.c.) and the chloride
328 mg. per 100 c.c. (normal, 340–80 mg. per 100 c.c.). A large excess
excretion of Na over Cl was shown in Case 13, Fig. 5, and a smaller excess
by Case 3, Fig. 6, in spite of the very high plasma chloride. Table IX
shows the observations on Case 7. Here, on admission, the excretion of

chloride just exceeded the excretion of Na.   These observations are similar
to the findings of Gamble, Blackfan, and Hamilton (1924–5) in an acidosis
caused by ammonium sulphate.

We interpret this excessive loss of sodium as being due to the ketone
acids carrying out the base with them.   The excess of Na, at any rate in
Case 13, is more than can be explained by mere loss of body water, a factor

Hours after admission	4	8	12	16	20	24	28	32	36	40	44	48	52	56
Plasma Chlorides as mg. Cl./100 ccs.	348					378						379		
Alkali Reserve vols.%	19·5					51								
Serum Sodium as mg./100 ccs.	298					305						315		
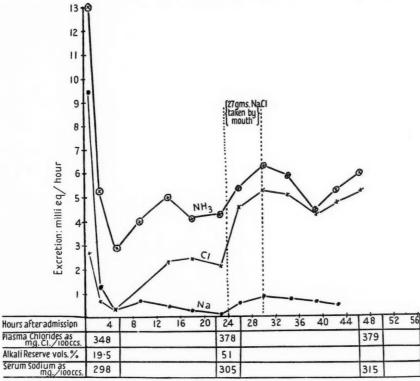
FIG. 5.

suggested by Gamble, Ross and Tisdall.   The degree of excess probably
depends upon the ammonia-forming capacity of the kidney, the degree and
duration of the ketosis and the diuresis, &c.   It is not due to high serum
sodiums, for these have always been found to be low, Figs. 5 and 6, Table III
[compare also Atchley and Benedict (1930–1), Hartmann and Darrow
(1928–9)].   As soon as treatment removes the ketosis the body is left with
a deficiency both of sodium and chloride, but with a relative deficiency of
sodium, and whether salt (saline) has been administered or not (Figs. 5
and 6) the excretion of chloride has always been observed to rise above that
of sodium.   Hartmann and Darrow (1928–9) suggested that this might take
place from their study of the plasma electrolytes in cases of severe diabetic
acidosis, which were being treated by insulin, water, and carbohydrate—but

no salt. We cannot be sure in all our cases whether this chloride came from the food or the tissues, but at any rate in Case 13, Fig. 5, nothing but glucose drinks and lemonade were administered, which suggests an origin in the tissues. At all events, when sodium chloride was given by mouth large amounts of chloride were at once excreted with ammonia, Figs. 5 and 6. Case 7, Table IX, was given copious injections of saline on admission. Case 2,

Day of observation	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Alkali Reserve Vols %	28		24·6		31		30·3		26·5		31·3			39	50		
Plasma Chlorides as mg. of Cl/100ccs	438		420		370		352		349		352			362	352		
Serum Sodium mg. Na/100ccs	317		318		308		297		302		302						
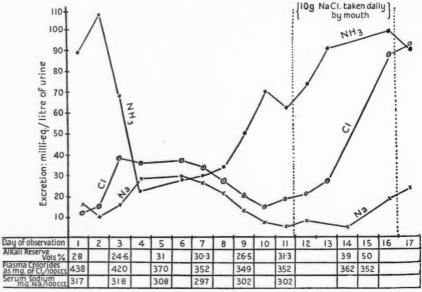
Fig. 6.

Fig. 2, demonstrates how great the shortage of sodium may be, for the alkali reserve took over a fortnight to reach normal in the absence of intensive saline therapy. Case 3 still had an alkali reserve of only 31·3 vols. per cent. eleven days after admission (Fig. 6) although the patient seemed perfectly well. Ten gm. of salt per day then led to considerable sodium retention and a rise in the alkali reserve to 50 vols. per cent.

It is obvious that a complete discussion of these results must involve the consideration of all the humoral acid-base regulating mechanisms, but we would rather limit the discussion to its bearing on the function of the kidney. The daily excretion of chloride has been observed to fall when oliguria has set in, and to this extent its excretion, and that of sodium, may be regarded as sharing in the functional disorganization. On the other hand, our results—so far as they go—do not suggest that the kidney has lost any of the acid-base regulating mechanisms associated with these ions. The processes outlined above seem to go on regardless of the failure or recovery of the nitrogen and water excretion (compare Figs. 3 with 5 and Fig. 6 with Table III). We suggest, therefore, that this function of the kidney is not impaired so long as the water excretion is maintained.

Discussion

Suggested causes of disordered renal function. We are unable to put forward any complete explanation, but our observations make it clear that many suggested hypotheses are untenable. The chief causes that have been suggested for the oliguria, high blood urea, &c., are :

1. *Dehydration*, due to acidosis, diuresis, vomiting, and air-hunger. This is certainly important before treatment and, if proved by high plasma proteins and increased haemoglobin, would be expected to produce oliguria and perhaps some rise of blood urea, but not the dilute urine found in these cases. However, increase of the plasma proteins to more than one and a half times the normal has never been recorded, and therefore dehydration alone cannot explain any increase of blood urea above this. Moreover, the plasma proteins have been normal or low in our cases of post-coma oliguria and nitrogen retention. Anhydraemia has been absent and therefore cannot explain the dysfunction.

2. *Failing circulation and low blood-pressure*, known to cause nitrogen retention, have been absent in most of our comatose and all of our post-coma cases.

3. The *overproduction of urea* following the excessive catabolism of protein in intense diabetes has not often been mentioned, but our results suggest that it must sometimes contribute to the high blood ureas met with before treatment.

4. *Insulin* has been suggested as a cause, mainly because the post-coma renal failure has been much more commonly observed since insulin was introduced (Rabinowitch (1928) and Bayer (1930)). Ehrmann and Jacoby (1925) and Lawrence and Hollins (1928) have pointed out that insulin may occasionally cause haematuria, but examination of the vast majority of well treated diabetics who are taking insulin shows that it has no real deleterious effect on the kidney. Again, mild signs of renal deficiency during coma are quickly relieved by insulin (Bulger and Peters, 1925). Moreover, true renal disorganization was demonstrated before the days of insulin (Fitz, 1917 ; McCay 1919–20). Any direct action of insulin on the kidney may therefore be excluded.

It has been suggested that insulin may act indirectly in causing oliguria, and hence kidney disturbance, in two ways. First, by abolishing glycosuria and re-establishing a glycogen store ; this undoubtedly promotes water retention, and Weiss (1927) goes so far as to suggest that it enables the body to store water so fast that the kidney becomes dehydrated and ceases to act. It is not clear, however, why the kidney should be dehydrated at this stage when anhydraemia is absent. Secondly, it has been suggested that insulin (whether sodium bicarbonate has been given or not) may so remove the acidosis and change the pH of the blood and tissues to the alkaline side that acute retention of water takes place with resulting oliguria. This has certainly been excluded in our cases in which a very

dilute and acid urine has invariably accompanied the post-coma oliguria and nitrogen retention.

We would suggest that if insulin does cause urea retention, it operates in the following way. The sudden restoration of carbohydrate metabolism demands the retention of a large volume of water. In the absence of enough electrolytes to bring this retained water up to the osmotic pressure of the body, urea is retained to regulate the osmotic pressure.

5. *The ketone bodies.* The direct injury to the kidney by these bodies during excretion, or the acidity produced by them, has been put forward by many authors, including Snapper (1927–8), and is difficult to exclude entirely as a factor in producing kidney failure. However, we consider their effect is inconsiderable on the following grounds :

(i) There is no experimental proof that these bodies are toxic to the kidney and, if they were, one would expect to find definite and uniform pathological changes in the kidney (of which there is no evidence) comparable to the effects of uranium, mercuric chloride, and other recognized toxins.

(ii) A prolonged and severe ketosis may be unaccompanied by any signs of renal disorganization.

(iii) We have observed one case (No. 5) of severe nitrogen retention during coma in which the urine contained only traces of ketone bodies and the alkali reserve was 80 vols. per cent.

(iv) Ketone bodies have been rapidly removed in our cases by insulin, so that, if they do injure the kidney, the effect must be long lasting.

(v) They can play no part in the two cases of non-comatose renal disorganization which we have observed.

6. *Chloride deficiency.* The azotaemia has been ascribed entirely to the deficiency of Cl ions in the blood, i.e. a hypochloraemia (Christiansen and Holst (1929); Chabanier and Lobo-Onel (1931)). From this view-point the fall in chlorides is the primary event and the rise of blood urea is an attempt on the part of the organism to maintain its osmotic pressure (Blum, Grabar, and van Caulaert, 1929). Ni (1926) has shown that the blood chlorides vary inversely with the blood-sugar in depancreatized dogs, and Meyer-Bisch and his associates (1924, 1926, 1927, a.b.) have investigated the changes experimentally and uphold the low chloride hypothesis. Glass (1932), moreover, has shown that prolonged experimental vomiting may lead to a chloride deprivation which is associated with severe nitrogen retention. The alkalosis, however, simultaneously produced, makes the syndrome not quite comparable with that of a diabetic coma. Further consideration of the low chloride hypothesis shows that it is untenable, because low blood chlorides are not invariable in coma and retention of urea has been met with at normal or high levels of plasma chloride (Pelligrini (1931); Labbé and Boulin (1931); Ingram and Rudd (1932); Fullerton et al. (1932)). Our own cases illustrate this very well. Case 3, Table III, was admitted with very high plasma chlorides which fell steadily to normal as azotaemia

developed and remained normal throughout recovery. Case 1, moreover, was treated by injections of hypertonic saline when the azotaemia was starting without apparently influencing its course in any way. It is of course possible that insufficient quantities were administered.

As it stands, this theory may be dismissed, but a very similar one, postulating a deficiency of fixed base, i.e. of electrolytes generally, as the cause, would be much more satisfactory and might be correct.

Other causes. Without being able to suggest any definite theory we believe that the most constructive line of thought is to regard all these cases of renal disorganization associated with coma as being of one origin, and analogous to those met with in intestinal intoxication of experimental or clinical origin (Schoenthal et al., 1933). We have no doubt that very similar, if not identical, syndromes may be encountered apart from coma, and we have reported some incomplete observations on two such cases in this paper. Then it is helpful to compare the renal disorganization of advanced Addison's disease, and here we would point out the points of similarity between diabetic coma and the features of suprarenal destruction. Both have low blood-pressures, subnormal temperatures, vomiting, a tendency to cardiac failure, a deficiency of fixed base and renal disorganization. Lawrence (1930) and Labbé and Boulin (1933) have both emphasized the value of intravenous adrenalin in the treatment of severe coma.

In conclusion, we are inclined at present to look for a metabolic cause, such as a deficiency of fixed base, for the nitrogen retention associated with coma. This may possibly be brought about, not merely by the acidosis and diuresis, but also conceivably by a partial failure of the function of the suprarenal cortex.

Treatment

Since its discovery, massive injections of insulin have always been used to combat coma, and intravenous and subcutaneous salines have for long been used to overcome the dehydration. This has been very generally advised for the renal complication (Begg (1925); Raw (1930–1); Weiss (1927)) and often pushed to its uttermost. Thus John (1925) attributed the successful recovery of his patient to hypertonic saline. Root and Henson (1931) used hypertonic saline as a last resort in a patient with post-operative suppression of urine. The patient recovered. Root (1934) has treated the suppression of urine following coma in a similar way and with good results. Blum, Grabar, and van Caulaert (1928), believing that the azotaemia was not renal in origin, but due to hypochloraemia, treated their patients with sodium chloride. It is worth noting that had the cause been *hyponatraemia* the same treatment would have been successful. Coburn (1930) suggested besides salines, blood transfusions and any other device calculated to raise the blood-pressure. Meyer, Bisch, and Wohlenberg (1926) have advocated bicarbonate. Decapsulation has even been tried—unsuccessfully (Kraus and Seyle (1928)). Recently, Fullerton, Lyall, and

Davidson (1932) have employed hypertonic glucose and attribute their success to it.

Unfortunately, few authors have seen enough cases of renal disorganization during and after coma to appraise satisfactorily the value of their treatment. Many have seen but one or two cases, and in the event of their recovery have been inclined to attribute it to something they themselves have done, something unusual tried after the failure of the more common remedies and at about the time spontaneous recovery might be expected. It is worth noting that the three cases under our observation which exhibited severe post-coma nitrogen retention received no treatment other than insulin, carbohydrate, and fluids—and all recovered.

Prognosis

It should be noted that these cases of coma with high urea retention have earned the reputation of being usually, and according to some authors invariably, fatal. This is not so, as our results and several other recorded cases show. This may be the case if the blood urea is found initially to be very high, but as our results and those of other authors show, the outlook is reasonably good when the nitrogen retention does not begin till later. Treatment, especially when extreme oliguria is present, is always very difficult.

Summary

1. Diabetic coma may be accompanied or followed by a disorganization of renal function which is characterized by (a) an oliguria which is not invariable and often transitory; (b) a retention of urea, creatinine (and probably uric acid) which may outlast the oliguria by some days; (c) a retention of ketone bodies (if present); (d) a retention of sugar (if present above threshold limits); (e) a very acid urine (p H usually about 5); (f) a normal excretion of ammonia; (g) no loss of the acid base regulating mechanisms associated with salt excretion; (h) no constant anatomical lesion; (i) a tendency to recovery with absence of sequelae.

2. A similar and possibly identical syndrome has been met with in two non-comatose diabetics and may be relatively common and be closely allied to the renal dysfunctions of intestinal intoxication and Addison's disease.

3. The real cause is unknown.

4. There is no specific treatment. If the patient lives, insulin and fluids (especially perhaps salines) will in time restore the function of the kidney.

REFERENCES

Abraham, A., and Altmann, M., *Klin. Wchnschr.*, Berl., 1927, vi. 2419.

Ambard, Merklen, Schmid, Wolf, and Arnovljevitch, *Bull. et mém. Soc. med. hôp. de Paris*, 1925, sér. 3, xlix. 547.

Appel, K. E., and Cooper, D. A., *Amer. Journ. Med. Sci.*, Philad., 1927, clxxiii. 201.

Archer, H. E., and Robb, G. D., *Quart. Journ. Med.*, Oxford, 1925, xviii. 274.

Argy, W. P., *Boston Med. and Surg. Journ.*, 1925, cxciii. 1236.

Aszodi, Z., *Biochem. Ztschr.*, Berl., 1928, cxcii. 26.

Atchley, D. W., and Benedict, E. M., *Journ. Clin. Invest.*, N. York, 1930–31, ix. 265.

Bayer, L. M., *Amer. Journ. Med. Sci.*, Philad., 1930, clxxix. 671.

Beaumont, G. E., and Dodds, E. C., *Recent Advances in Medicine*, Lond., 3rd ed., 1926.

Begg, A. C., *Lancet*, Lond., 1925, ii. 69.

Bernard, E., and Guillaumin, *Bull. et mém. Soc. med. hôp. de Paris*, 1933, sér. 3, xlix. 330.

Blum, L., Grabar, P., and van Caulaert, *Presse méd.*, Paris, 1928, lxxxix. 1411.

Blum, L., Grabar, P., and van Caulaert, *Ann. de méd.*, Paris, 1929, xxv. 34.

Born, *Korrespondenzbl. f. schweitz. Aerzte*, Basel, 1892, xxii. 347.

Bouchardat, M., *Compt. rend. d'acad. de sci.*, Paris, 1845, xx. 1020.

Bowen, and Beck, *Bull. Buff. Gen. Hosp.*, 1925. Quoted by Joslin, Root, and White.

Brull, L., and Roersch, C., *Biochem. Journ.*, Camb., 1934, xxviii. 1513.

Brunton, C. E., *Brit. Med. Journ.*, Lond., 1924, ii. 665.

Bulger, H. A., and Peters, J. P., *Arch. Int. Med.*, Chicago, 1925, xxxvi. 857.

Bulow Hansen, V., *Acta Med. Scand.*, Stockholm, 1929, lxxii. 399.

Cawley, T., *Lond. Med. Journ.*, 1788, ix. 286.

Chabanier, H., and Lobo-Onel, C., *Précis du Diabète*, Paris, 1931, 247.

Chabanier, H., Lebert, M., Lobo-Onel, C., and Lumiere, F., *Presse méd.*, Paris, 1927, xxxv. 83.

Chauffard, A., and Rendu, H., *Rev. de méd.*, Paris, 1912, xxxii. 417.

Christiansen, O., and Holst, J. E., *Ztschr. f. klin. Med.*, Berl., 1929, cxi. 88.

Coburn, A. F., *Amer. Journ. Med. Sci.*, Philad., 1930, clxxx. 178.

Colin, *Gaz. Hebdomad. Med. Chir.*, Paris, 1868, sér. 2, v. 467.

Dinkin, L., *Klin. Wchnschr.*, Berl., 1927, vi. 1330.

Dolore, P., *Presse méd.*, Paris, 1925, xxxiii. 52.

Domanski, H., and Reimann, G., *Ztschr. f. Heilk.*, Wien, 1901, xxii, *Abt. f. Int. Med.*, 226.

Dreschfeld, J., *Brit. Med. Journ.*, Lond., 1881, ii. 709.

Dreschfeld, J., *ibid.*, 1886, ii. 358.

Ebstein, W., *Deutsches Arch. f. klin. Med.*, Leipz., 1881, xxviii. 143.

Ehrmann, R., and Jacoby, A., *Klin. Wchnschr.*, Berl., 1925, iv. 2151.

Elmer, A. W., and Scheps, M., *Deutsches Arch. f. klin. Med.*, Leipz., 1928, xlxii. 144.

Elmer, A. W., and Scheps, M., *Klin. Wchnschr.*, Berl., 1930, ix. 1631.

Epstein, A. A., and Baehr, G., *Journ. Biol. Chem.*, Balt., 1916, xxiv. 1.

Epstein, A. A., Reiss, J., and Branower, J., *ibid.*, 1916, xxvi. 25.

Evans, G., *Lancet*, Lond., 1925, i. 77.

Feinblatt, H. M., *Arch. Int. Med.*, Chicago, 1924, xxxiv. 508.

Fichtner, R., *Virchows Archiv.*, Berl., 1888, cxiv. 401.

Fichtner, R., *Deutsches Arch. f. klin. Med.*, Leipz., 1889, xlv. 112.

Fitz, R., *Arch. Int. Med.*, Chicago, 1917, xx. 809.

Fitz, R., and Van Slyke, D. D., *Journ. Biol. Chem.*, Balt., 1917, xxx. 389.

Foster, B., *Brit. Med. Journ.*, Lond., 1878, i. 78.

von Frerichs, F. T., *Uber den Diabetes*, Berl., 1884, 120.

Fullerton, H. W., Lyall, A., and Davidson, L. S. P., *Lancet*, Lond., 1932, i. 558.

Gamble, J. L., Blackfan, K. D., and Hamilton, B., *Journ. Clin. Invest.*, N. York, 1924–25, i. 359.

Gamble, J. L., Ross, G. S., and Tisdall, F. F., *Journ. Biol. Chem.*, Balt., 1923, lvii. 633.

Glass, J., *Ztschr. f. d. exper. Med.*, Berl., 1932, lxxxii. 776.

Gottschalk, A., and Muller, O., *Klin. Wchnschr.*, Berl., 1930, ix. 1204.

Graham, G., Spooner, E. C. T., and Smith, W., *St. Bart.'s Hosp. Rep.*, Lond., 1929, lxii. 55.

Harrison, G. A., *Chemical Methods in Clinical Medicine*, Lond., 1930.

Hartmann, A. F., and Darrow, D. C., *Journ. Clin. Invest.*, N. York, 1928–29, vi. 257.

Hawk, P. B., *Practical Physiological Chemistry*, Lond., 1923, 8th ed.

Hesse, J., *Berl. klin. Wchnschr.*, Berl., 1888, xxv. 379.

Hugounenq, Morel, and Froment, *Büll. et mém. Soc. méd. hôp. de Paris*, 1913, sér. 3, xxxv. 951.

Imrie, C. G., and Skinner, E. F., *Lancet*, Lond., 1924, i. 14.

Ingram, W. W., and Rudd, G. V., *Med. Journ. of Australia*, Glebe, N.S.W., 1932, ii. 204.

John, H. J., *Journ. Amer. Med. Assoc.*, Chicago, 1925, lxxxiv. 1400.

Joslin, E. P., *The Treatment of Diabetes Mellitus*, 3rd ed., Philad., 1924, 373.

Joslin, E. P., *ibid.*, 4th ed., 1928, 439.

Joslin, E. P., Root, H. F., and White, P., *Med. Clin. N. Amer.*, Philad., 1927, x. 1281.

Joslin, E. P., Root, H. F., White, P., Marble, A., and Hunt, H. M., *ibid.*, 1933, xvi. 793.

Jungmann, H., *Med. Klin.*, Berl., 1926, xxii. 2032.

Kaulich, J., *Prager Vierteljahrschr.*, 1860, lxvii. 58.

Kraus, E. J., and Seyle, H., *Klin. Wchnschr.*, Berl., 1928, vii. 1627.

Kuhn, R., and Witscher, L., *ibid.*, 1931, x. 1616,

Labbé, M., and Boulin, R., *Ann. méd.*, Paris, 1931, xxix. 386.

Labbé, M., and Boulin, R., *Bull. et mém. Soc. méd. hôp. de Paris*, 1931, xlvii. 223.

Labbé, M., and Boulin, R., *Presse méd.*, Paris, 1933, xli. 1703.

Lawrence, R. D., *Brit. Med. Journ.*, Lond., 1930, i. 690.

Lawrence, R. D., and Hollins, A. S., *ibid.*, 1928, i. 977.

Lemann, I. I., *Med. Clin. N. Amer.*, Philad., 1926, ix. 989.

Lepine, R., *Rev. de méd.*, Paris, 1897, xvii. 832.

Lepine, R., *Le diabéte sucré*, Paris, 1909, 693.

Linder, G. C., *Quart. Journ. Med.*, Oxford, 1926–27, xx. 285.

Lion, Chabanier, H., and Minvielle, *Bull. et mém. Soc. méd. hôp. de Paris*, 1924, sér. 3, xlviii. 110.

Lorant, J. St., *Acta Med. Scand.*, Stockholm, 1929, lxx. 216.

Löwenberg, W., and Joel, W., *Klin. Wchnschr.*, Berl., 1928, vii. 2203.

Lyall, A., and Anderson, A. G., *Quart. Journ. Med.*, Oxford, 1932, New Ser. 1, 353.

McCance, R. A., and Shipp, H. L., *Med. Res. Coun. Spec. Rep. Ser.*, Lond., 1933, clxxxvii.

McCance, R. A., and Watchorn, E., *Quart. Journ. Med.*, Oxford, 1931, xxiv. 371.

McCann, *N. York State Journ. Med.*, 1925, xxv. 200.

McCaskey, G. W., *Journ. Amer. Med. Assoc.*, Chicago, 1915, lxvi. 350.

McCay, D., *Indian Journ. Med. Res.*, Calcutta, 1919–20, vii. 22.

Marischler, J., *Arch. f. Verdauungskr.*, 1901, vii. 332.

Magnus-Levy, A., and Siebert, W. W., *Ztschr. f. klin. Med.*, Berl., 1928, cvii. 197.

Merklen, P., Wolf, M., and Bicart, P., *Bull. et mém. Soc. méd. hôp. de Paris*, 1926, sér. 3, i. 359.

Metzger, H., *Med. klin.*, Berl., 1927, xxiii. i. 598.

Meyer-Bisch, R., and Bock, D., *Ztschr. f. d. exper. Med.*, Berl., 1927, liv. 131.

Meyer-Bisch, R., and Bock, D., *ibid.*, 1927, liv. 145.

Meyer-Bisch, R., and Gunther, F., *Biochem. Ztschr.*, Berl., 1924, clii. 286.

Meyer-Bisch, R., and Wohlenberg, W., *Ztschr. f. klin. Med.*, Berl., 1926, ciii. 260.

Mördre, S. K., *Acta Med. Scand.*, Stockholm, 1921, lv. 511.

Nash, T. P., and Benedict, S. R., *Journ. Biol. Chem.*, Balt., 1921, xlviii. 463.

Nebelthau, *Aertz. Verein zu Marburg. Berl. klin. Wchnschr.*, Berl., 1896, xxxiii. 771.

Ni, T. G., *Amer. Journ. Physiol.*, Balt., 1926, lxxviii. 158.

von Noorden, C., *Die Zuckerkrankheit und ihre Behandlung*, Berl., 1912, 227.

Oliver, T. H., *Lancet*, Lond., 1926, i. 750.

Paddock, *Journ. Amer. Med. Assoc.*, Chicago, 1924, lxxxii. 1885.

Palmer, W. W., and Henderson, L. J., *Arch. Int. Med.*, Chicago, 1915, xvi. 109.

Payne, W. W., and Poulton, E. P., *Lancet*, Lond., 1925, ii. 638.

Pelligrini, G., *La Riforma Med.*, Naples, 1931, ix. 875.

Peters, J. P., Kydd, D. M., Eisenman, A. J., and Hald, P. M., *Journ. Clin. Invest.*, N. York, 1933, xii. 377.

Peters, J. P., and Van Slyke, D. D., *Quantitative Clinical Chemistry*, Lond., 1931, ii. 370.

Petters, W., *Prager Vierteljahrschr.*, 1857, lv. 81.

Rabinowitch, J. M., *Arch. Int. Med.*, Chicago, 1924, xxxiii. 394.

Rabinowitch, J. M., *Canad. Med. Assoc. Journ.*, Montreal, 1929, New Ser. xxi. 274.

Rachmilewitz, M., *Lancet*, Lond., 1934, i. 78.

Rau, H., *Ztschr. f. Kinderheilk*, Berl., 1930–31, i. 119.

Rehberg, P. B., *Biochem. Journ.*, Camb., 1926, xx. 447.

Revillet, *Lyon Med.*, Lyon, 1914, cxxii. 815.

Root, H. F., *Journ. Amer. Med. Assoc.*, Chicago, 1934, ciii. 482.

Root, H. F., and Henson, P. P., *ibid.*, 1931, xcvii. 541.

Rosenbloom, J., *N. York State Journ. Med.*, 1915, cii. 294.

Roth, E., *Wien. klin. Wchnschr.*, 1929, xlii. 1190.

Rudy, A., and Levin, C. M., *N. York State Journ. Med.*, 1927, xxvii. 1240.

Rumpf, T., *Berl. klin. Wchnschr.*, Berl., 1895, xxxii. 669.

Salomonson, L., and Harboe, M., *Acta Med. Scand.*, Stockholm, 1925–26, lxiii. 425.

Salvesen, H. A., *ibid.*, 1928, lxix. 126.

Sandmeyer, W., *Verhandl. des Congresses für inn. Med.*, Wiesb., 1891, x. 341.

Schoenthal, L., Lurie, D., and Kelly, M., *Amer. Journ. Dis. Child.*, Chicago, 1933, xlv. 41.

Sezary, Chabanier, H., Lobo-Onel, C., Lebert, M., and Grove, M. E., *Bull. et mém. Soc. méd. hôp. de Paris*, 1923, sér. 3, xlvii. 1010.

Van Slyke, D. D., *Journ. Biol. Chem.*, Balt., 1923–24, lviii. 523.

Van Slyke, D. D., Linder, G. C., Hillier, A., Leiter, L., and McIntosh, J. F., *Journ. Clin. Invest.*, N. York, 1925–26, ii. 255.

Snapper, J., *Med. Klin.*, Berl., 1927, xxiii. 897.

Snapper, J., *Proc. Roy. Soc. Med.*, Lond., 1928, xxi. 1771.

Starr, P., and Fitz, R., *Arch. Int. Med.*, Chicago, 1924, xxxiii. 97.
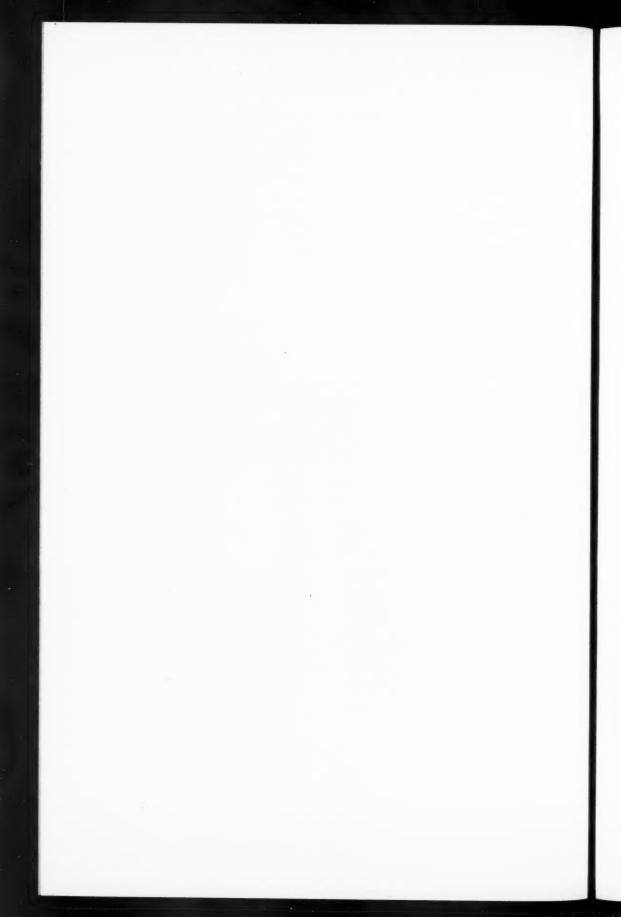
Strothman, H., *Deutsches Arch. f. klin. Med.*, Berl., 1928, clxii. 118.

Warburg, E., *Acta Med. Scand.*, Stockholm, 1924–25, lxi. 301.

Warren, S., *The Pathology of Diabetes Mellitus*, Philad., 1930, 116.

Weiss, T., *Deutsches Arch. f. klin. Med.*, Leipz., 1927, clvi. 226.

Wolpe, H., *Arch. f. exper. Path. u. Pharm.*, Berl., 1886, xxi. 154.

PRIMARY LYMPHOGRANULOMA OF THE STOMACH [1]

A REPORT OF FOUR NEW CASES

By THEODORE THOMPSON and LEONARD H. HOWELLS
(From the London Hospital)

With Plate 8

Introduction

LYMPHOGRANULOMA or so-called lymphosarcoma may occur in the stomach either as an isolated primary lesion or in association with involvement of other tissues throughout the body. We propose to deal only with the rare localized form, which may be an ulcer or a tumour-like mass, because there is evidence that partial gastrectomy is often followed by excellent results. The diagnosis can be established only by a microscopic examination; in none of the recorded cases had it been suspected prior to operation or a post-mortem examination; all of them had been diagnosed either as carcinoma or a chronic ulcer of the stomach.

A search in the literature revealed about thirteen cases in which a localized lesion was found in the stomach. Partial gastrectomy was successfully performed upon nine of these, and four others died after the operation.

The first case was described by Ruppert (1912). This was a woman, aged 58, who was found to have a lymphosarcoma after partial gastrectomy had been performed for supposed carcinoma. There was no evidence of recurrence fourteen and a half years later. No further cases were recorded until 1924, when Knazelson (1924) reported a case where the clinical and radiological finding favoured a diagnosis of malignant ulcer producing partial occlusion of the pylorus. At the post-mortem examination he found a lymphogranulomatous ulcer, partly in the prepyloric antrum and partly in the duodenum, with a second ulcer on the anterior wall of the stomach. In the following year Neuber (1925) recorded one in which a chronic gastric ulcer proved to be lymphogranulomatous on microscopic examination. Soon after this Steindl (1925) described a case thought to be the first recorded in which a lymphogranuloma localized to the stomach was operated upon successfully. This has since been followed by others reported by von Redwitz (1926), Froboese (1927), Freeman (1928), Vasiliu (1929), Cheever (1932), and Hunt

[1] Received July 13, 1934.

(1932). Kan (1926) described a case upon whom partial gastrectomy was performed for supposed carcinoma. The patient died, and at necropsy there was no naked-eye evidence of disease elsewhere. On microscopic examination the mass in the stomach proved to be a lymphogranuloma.

Singer (1931) also recorded a similar case. At operation a mass was discovered in the stomach, and gastro-enterostomy was accordingly performed. The patient died, and at autopsy the gross and microscopic appearances of the stomach and perigastric glands were those of lymphogranuloma. No evidence of foci elsewhere was found.

Mittelbach (1932) has reported a similar case. Partial gastrectomy was performed for a supposed chronic peptic ulcer, which was later found to have the histological features of Hodgkin's disease. The post-mortem examination showed no further evidence of the disease, apart from one metastasis in an epigastric gland.

More often the lesion spreads into the neighbouring glands, thus rendering surgical treatment impracticable. Such cases may be described as regional in distribution, for distant organs and glands are apparently free from involvement.

Klopstein (1933) mentioned a typical instance where a patient, thought to have a gastric carcinoma, died after partial gastrectomy. Lymphogranulomatous deposits were found in the excised stomach, retroperitoneal glands, and spleen at autopsy.

Similar cases where there has been involvement of abdominal glands have been fully recorded by Scott and Foreman (1916), Drope (1926), Hayden and Apfelbach (1927), Tschilow (1929), Sussig (1929), and Ramond et al. (1930). Operation had not been attempted in any of these, and the diagnosis was established on microscopic evidence. One patient described by Drope died from perforation of the ulcer.

Walters and Church (1934) have reported a case of lymphosarcoma of the stomach with involvement of the lymph glands, in which the growth had perforated through the mesocolon to the pancreas. Removal of the growth was followed by complete relief of symptoms, and the patient was well three years later.

The stomach is not often affected when the disease is primarily distributed in other parts of the body, but examples of this are on record.

Pitt (1889) first described the presence of lesions in the stomach and duodenum in association with widespread Hodgkin's disease. Reimann (1917) mentioned a similar case in whom there were four ulcers in the stomach. Sternberg (1925) reported an interesting case who died from Hodgkin's disease of the stomach. The patient had been treated by X-ray therapy for a mediastinal mass six years previously, and although Sternberg considered that this was undoubtedly lymphogranulomatous, no trace of it could be found at autopsy. Another remarkable case was described by Harper (1932). A cervical gland, which proved to be a lymphosarcoma, had been excised thirteen years previously. The caecum was excised because of a similar

tumour nine years previously. In 1932 the patient complained of recent dyspepsia, and after partial gastrectomy a lymphosarcomatous tumour was found in the stomach. The patient survived !

Our attention was directed to the apparently localized form of lymphogranuloma or so-called lymphosarcoma of the stomach, by a patient who recently came under the care of one of us (Theodore Thompson). A search of the records of the London Hospital from 1920 to 1934 has revealed three similar cases (Appendix), and in all the true diagnosis was established only after microscopic examination. Professor Hubert M. Turnbull has kindly examined and fully reported upon the macroscopic and microscopic appearances of the excised portion of stomach and neighbouring glands in the four cases (see Appendix). The differentiation between the histological changes in Hodgkin's lymphogranuloma and lymphosarcoma is very difficult. Turnbull (1929) believes lymphosarcoma to be a lymphogranuloma rather than a neoplasm and to be akin to Hodgkin's lymphogranuloma. According to him two of our cases proved to be examples of lymphogranuloma without involvement of the regional lymphatic glands (Cases 1 and 4), one was a so-called large-celled lymphosarcoma or lymphogranuloma with involvement of the regional lymphatic glands (Case 2), and the other was a so-called small-celled lymphosarcoma or lymphogranuloma with an outlying nodule of infiltration in the great omentum (Case 3). The histological features were not quite characteristic of Hodgkin's lymphogranuloma, although there were many points of similarity.

Clinical Aspect

The condition occurs most commonly between the ages of 40 and 60 years. Drope (1926) found that 55 per cent. were between 40 and 50 years, and 20 per cent. between 20 and 30 years of age. Cheever (1932) reported nine cases of lymphosarcoma, and found the average age was 56 years. Hunt (1932) recorded the occurrence in a patient aged 3 years 8 months. The ages in our series were 39, 42, 52, and 58 years respectively.

The chief symptoms are epigastric discomfort or pain of varying severity after food, loss of appetite, loss of weight and strength, flatulence, nausea and vomiting, haematemesis and melaena. These may be of recent onset and rapid progress, or have existed for many years with periodic remissions. The presenting symptoms in each of our patients were those of dyspepsia of short duration in two, and of longer duration in two. In one of these there were intervals of freedom from pain. Melaena was a prominent feature in one patient.

On physical examination there are usually no abnormal signs, except for emaciation in some patients. A palpable epigastric tumour is rare, but it was present in one of our patients, and was thought to be a gastric carcinoma. Sometimes there may be irregular pyrexia, but this is not common. It was observed in one of our cases after a previous appendicectomy. Apart

from occasional mild secondary anaemia, there are no typical changes in the blood count; one of our patients was anaemic after recurrent melaena. The gastric acidity varies; there was achlorhydria in one and a normal gastric acidity in two of our patients.

Diagnosis. The radiological findings are usually those of carcinoma or chronic ulcer of the stomach, without any special features to aid diagnosis, although Junghagen (1927), Coronini (1928), and Knazelson (1924) have claimed that lymphogranuloma of the stomach can be suspected sometimes from the radiological appearances. The majority of observers, including Holmes, Dresser, and Camp (1926) and Klopstein (1933) maintain that this is not possible. The results of a barium meal suggested the presence of gastric carcinoma in one, and lesser curve ulcer in two of our patients.

The clinical and radiological findings therefore usually indicate a diagnosis of gastric carcinoma or gastric ulcer, and a laparotomy is often performed on this assumption. This is even supported by the naked·eye appearances of the stomach at operation, and as this tends to reduce the fuller exploration of the abdomen, diagnostic information which might have been obtained, is often lacking in those patients who survive. In the present series a diagnosis of carcinoma ventriculi was made in three, and of chronic gastric ulcer in one, prior to operation. Evidence suggesting carcinoma in three, and chronic ulcer in one, was encountered during laparotomy. Partial gastrectomy with excision of the neighbouring glands was performed in all four.

Treatment. Partial gastrectomy and excision of the neighbouring glands is probably the best form of treatment. Some details of cases, collected from the literature, who have benefited from this operation are shown in the accompanying table. It can be seen that at least ten patients have recovered from the operation, and have shown no evidence of recurrence for periods varying up to fourteen and a half years. The table does not embrace a full résumé of the literature upon the subject because the uncertain nomenclature and incomplete case records make this task impracticable. The value of X-ray therapy in the treatment of lymphosarcoma of the stomach has been advocated by several writers, including Gunsett and Oberling (1928), Freeman (1928), Ruggles and Stone (1930), and Cheever (1932). These suggest that X-ray treatment may be followed by good results even when the condition has been inoperable, and that it should always be employed after partial gastrectomy.

The results after partial gastrectomy in the present series have certainly been encouraging. Case 1 is engaged in active work and shows no signs of recurrence fourteen years after the operation. Case 3 is leading a normal life, and there is no evidence of recurrence seventeen months later. It is too early to estimate the result in Case 4, who has been operated upon only recently. Case 2 appeared to improve for eight months, but she died presumably from further spread of the disease eleven months after the operation.

TABLE

Some Cases of Lymphogranuloma and So-called Lymphosarcoma Treated Successfully by Partial Gastrectomy

Author and date.	Clinical diagnosis.	Operation.	Result.	Microscopic diagnosis.	Remarks.
Ruppert 1912	Carcinoma ventriculi	Partial gastrectomy	Recovered. Alive 14½ years later	Lympho-sarcoma	Primary lesion confined to stomach
Neuber 1925	Chronic gastric ulcer	Partial gastrectomy	Recovered	Lympho-granuloma	Primary lesion confined to stomach
Steindl 1925	Carcinoma ventriculi	Partial gastrectomy	Recovered. Alive 1 year later	Lympho-granuloma	Primary lesion confined to stomach
von Redwitz 1926	Peptic ulcer	Partial gastrectomy	Recovered	Lympho-granuloma	Primary lesion confined to stomach
Froboese 1927	Carcinoma ventriculi	Partial gastrectomy	Recovered	Lympho-granuloma	Primary lesion confined to stomach
Freeman 1928	Carcinoma ventriculi	Partial gastrectomy	Recovered. Alive 1½ years later	Lympho-granuloma	X-ray therapy after operation
Vasiliu 1929	Chronic peptic ulcer	Partial gastrectomy	Recovered. Alive 3 years later	Lympho-granuloma	Primary lesion in stomach. Peri-gastric glands enlarged
Hunt 1932	Pyloric obstruction	Partial gastrectomy	Recovered	Lympho-sarcoma	Primary lesion confined to stomach
Cheever 1932	?	Partial gastrectomy	Recovered. Alive 6 years later	Lympho-sarcoma	Subsequent deep X-ray therapy. Primary lesion in stomach
Walters and Church 1934	Pyloric obstruction	Partial gastrectomy	Recovered. Alive 3 years later	Lympho-sarcoma	Involvement of regional lymph glands and mesocolon
Thompson and Howells 1934	Case I. Carcinoma ventriculi	Partial gastrectomy	Recovered. Alive 14 years later. No sign of recurrence.	Lympho-granuloma	Primary lesion confined to stomach
Thompson and Howells 1934	Case II. Carcinoma ventriculi	Partial gastrectomy	Recovered, but died 11 months later	So-called large-celled lympho-sarcoma	Primary lesion in stomach, with involvement of regional glands
Thompson and Howells 1934	Case III. Carcinoma ventriculi	Partial gastrectomy	Recovered. No signs of recurrence 17 months later	So-called large-celled lympho-sarcoma	Primary lesion in stomach, with involvement of regional glands
Thompson and Howells 1934	Case IV. Gastric ulcer	Partial gastrectomy	Recovered	Lympho-granuloma	Lesion confined to stomach

Prognosis. The prognosis is therefore good if partial gastrectomy and excision of the neighbouring glands is done early, and it may be further improved by subsequent deep X-ray therapy. It appears that deep X-ray therapy will prolong life and relieve symptoms even in cases considered to be inoperable, and this form of treatment should always be employed in such cases.

Case Reports

Case 1. C. A., male, aged 42. A carpenter. Was admitted to the London Hospital, under the care of Mr. Sherren, in July 1920.

History. He was quite well until four months previously, when he began to complain of aching pain two inches above the umbilicus, two hours after food. The pain awakened him three hours after retiring at night. It was relieved by food. He lost one and a half stone in weight. His appetite was good, and he had no vomiting, haematemesis, nor melaena.

Past history. Nothing of importance. *Physical signs.* He was a well-nourished man of healthy appearance. Heart, lungs, central nervous system normal. Abdomen.—The right kidney was palpable, but there was no other abnormal signs. There was no pyrexia.

Special Investigations.

Wassermann reaction. Negative. *Test meal.* Free hydrochloric acid 0·15 per cent. Total acidity 63. *Barium meal.* There was some spasm on the lesser curve near the pylorus. There was a persistent tender point with evidence of a penetrating ulcer about half-way along the lesser curve. At the end of two hours there was only a small amount of barium remaining in the stomach, and the evidence of a penetrating ulcer persisted. A diagnosis of carcinoma of the stomach was made.

13.7.20. At operation by Mr. Sherren a large hard ulcer adherent to the pancreas was found on the lesser curve and posterior surface of the stomach, about half-way between the pylorus and cardia. Many enlarged glands were present in the subpyloric region, mesocolon, great omentum, and lesser omentum. A partial gastrectomy was performed, and the ulcer appeared to be ' definitely cancerous to the naked eye '. *Fourteen years* later the patient kindly consented to come into hospital for full investigation. Since the operation he has been in good health apart from recurrence of pain and dyspepsia for a short period in 1932. The symptoms rapidly subsided with medical treatment by his own doctor. He has no symptoms at present, and is fully employed as a clerk.

Physical signs. The patient is a well-developed, healthy-looking man. No evidence of glandular enlargement. There are no abnormal signs in the heart, lungs, central nervous system, or abdomen, apart from a well-healed upper paramedian scar. *Fractional test meal.* Complete achlorhydria throughout. Total acidity 25. *Barium meal.* There is evidence of partial gastrectomy. The stoma works adequately. Nothing else abnormal. An X-ray of the chest revealed no abnormality.

Pathological Report

Professor Turnbull concluded his descriptions of the naked-eye and microscopical appearances as follows :—

In this specimen the condition is not obviously peptic ulceration of a lymphogranulomatous area. The question of a peculiar lymphogranulomatous reaction in the border of a chronic peptic ulcer has to be considered. The infiltration in the submucosa at the margins of the ulcer is much greater and more sharply defined than in ordinary peptic ulcers, and is associated with great rarefaction of the collagenous stroma. Although the dense fibrosis in the floor of the ulcer shows that it is chronic, the mucosa with the muscularis mucosae is not approximated to the muscularis at the edge of the ulcer, as is the case in simple chronic progressive peptic ulceration, but on the contrary it is widely separated from it by the lymphoid tissue, as is the case with secondary peptic ulceration of a carcinoma. The lymphoid tissue formed to the naked eye a tumour-like mass in the submucosa at the margins of the ulcer, while a discrete nodule, 2 cm. in diameter and free from ulceration, lay in its neighbourhood. Further, it was found microscopically to be associated with the enlargement of the lymph follicles in the adjacent mucosa. It appears to be, and was originally diagnosed as, an example of peptic ulceration of a lymphogranuloma akin to those in Cases 2 and 3, but without involvement of the regional glands. It has not the characteristics of Hodgkin's lymphogranuloma.

Case 2. J. C., female, aged 52 years. The patient was admitted to the London Hospital, under the care of Mr. Souttar, in August 1927.

History. For eight months she had experienced pain in the right hypochondrium after food. Her appetite was poor, and she had lost weight. There was occasional vomiting.

Past history. Typhoid fever in 1892. She had an attack of ' indigestion ' five years previously, for which her teeth were removed. *Physical signs.* Healthy appearance. There was a tender swelling in the left hypochondrium. No abnormal signs in the heart, lungs, and nervous system.

Special Investigations.

Test meal. No free hydrochloric acid. Total acidity 40. *Barium meal.* Low stomach of poor tone. Lesser curve normal. Large defect with irregularity of pars pylorica. Definite delay in emptying. The duodenum was difficult to fill on account of condition of pylorus, but appeared normal. Radiological evidence of carcinoma of pars pylorica. The diagnosis was carcinoma of the stomach.

Operation. A laparotomy was performed by Mr. Souttar 9.3.27. A large mass, thought to be carcinomatous, was found starting high up on the lesser curve of the stomach, with secondary glands in the lesser omentum. No deposits seen in the liver or portal fissure. Partial gastrectomy was performed.

Further course. The patient recovered from the operation, and was quite well for eight months. The husband has written to say that she then became ill and died at home eleven months after the operation. No postmortem available.

Pathological Report

Professor Turnbull concluded his descriptions of the naked eye and micro-scopical appearances as follows:—

The lesion in this specimen is undoubtedly peptic ulceration of a tumour-like mass of lymphocytic infiltration of the stomach, associated with similar infiltration of the regional lymphatic glands. The tumour is an example of what is often called large-celled lymphosarcoma. Lymphosarcoma differs, however, in many important respects from a true neoplasm in the restricted sense (Turnbull (1929)). I believe lymphosarcoma to be a lymphogranuloma rather than a neoplasm, and to be akin to Hodgkin's lymphogranuloma. In examples of Hodgkin's disease the lesions in some parts of the body may in part or throughout be indistinguishable from lymphosarcoma. This suggests that cases in which lymphosarcoma is alone present are aberrant forms of Hodgkin's disease. It is difficult, however, to accept this conclusion, because the adenoid tissue of the intestine is affected so frequently in cases of pure lymphosarcoma and so rarely in Hodgkin's disease. In the present state of knowledge, therefore, a diagnosis of Hodgkin's disease is justifiable only when its characteristic histological changes are found in at least some of the infiltrated areas in the body. Although a few giant cells of Hodgkin type were found in the regional lymphatic glands, the lymphogranuloma in this case cannot be said to show the characteristic histological picture of Hodgkin's lymphogranuloma.

Case 3. F. C., male, aged 58 years. A private secretary. The illness commenced in 1928, when the patient fainted and later passed black motions. Following this he experienced heartburn and indigestion, coming on some little time after food and temporarily relieved by food and alkalis. He also experienced discomfort over the lower end of the sternum, as if food stuck before entering the stomach.

On October 24th, 1931 the patient fainted while at stool and passed a black motion. Later he vomited a large quantity of altered blood. Two days later the nurse reported that he passed a large quantity of red-black stool (two quarts) following a rectal washout. He was treated with a modified Hurst régime, and although his pallor persisted he improved, and there was no further visible bleeding. His appetite was poor. Weight constant.

Past history. He has experienced ' heart burn ' for about forty years. No real pain. Appendicectomy in 1914.

Physical examination. Apart from pallor, there were no abnormal signs in the heart, lungs, abdomen, or nervous system.

Special Investigations.

Barium meal. There was no definite evidence of gastric or duodenal ulcer or neoplasm. *Blood count.* Red cells 3,940,000, haemoglobin 45 per cent., colour index 0·56. In November 1932, however, the faintness and bleeding recurred on one occasion.

The patient was examined by one of us (Theodore Thompson) and thought to be suffering from a bleeding duodenal ulcer or gastric neoplasm. A laparotomy was therefore advised. In December 1932 an operation was performed by Mr. Perry. A tumour, which appeared to be cancerous to the naked eye, was found in the stomach, and the perigastric glands were enlarged. There was no sign of further disease at operation. Partial gastrectomy was performed.

Post-operative course. Apart from pulmonary complications he did well, and was discharged in January 1933, i.e. four weeks after the operation.

Second examination. The patient was re-examined in May 1934, that is, seventeen months after the operation. He gradually returned to his normal duties, and felt quite well. He has experienced dull aching umbilical pain without definite relationship to meals. His appetite is fairly good, and he has lost two stone in weight, but the latter is probably accounted for by a restricted diet. No other symptoms.

Physical examination revealed no abnormality in the heart, lungs, central nervous system, and abdomen apart from the operation scars.

Pathological Report

Professor Turnbull concluded his descriptions of the naked-eye and microscopical appearances as follows :—

In this specimen there is slight focal superficial ulceration near the centre of a massive infiltration of the stomach and great omentum with so-called small-celled lymphosarcoma, or lymphogranuloma (Turnbull (1929)). There is no trace of the histological characteristics of Hodgkin's lymphogranuloma.

Case 4. W. P., male, aged 39 years. A bank clerk, was admitted to the London Hospital under the care of Mr. Walton on June 24th, 1932.

History. For two years he had complained of attacks of epigastric pain about four to five hours after food, with one remission. The pain was never severe, and was not relieved by taking food. For one week he had been constipated and experienced a different pain around the umbilicus. On the day before admission the pain became much more severe, and settled in the right iliac fossa.

Past history. Dysentery in army 1915. Burn on right forearm 1929.
Physical signs. The patient looked ill. Temperature 99° F. Pulse rate 96. Abdomen—Tenderness and rigidity over McBurney's point. No other abnormal signs in abdomen, heart, lungs, and central nervous system. He was thought to have appendicitis, and an emergency laparotomy was accordingly performed by the resident surgeon. The appendix appeared to be inflamed and was removed. A large hard lump was palpated under the anterior abdominal wall, so a right upper paramedian incision was made. Two hard calcified glands were discovered in the mesentery, and a large mass adherent to the greater curvature in the region of the pyloric antrum. There was no evidence of an ulcer crater, and a portion of the mass was excised for histological section. Gall bladder normal.

Post-operative course. There was an irregular pyrexia 97·5° to 102·5° F. for three weeks. The temperature gradually subsided and was normal on his discharge to a convalescent home on 26.7.32. He eventually 'did well'. The Wassermann reaction was negative. The microscopic examination showed slight chronic inflammation of the appendix and old fibrosis obliterating the lumen focally ; there was a granulating abscess in the adipose tissue from the greater curve of the stomach.

Second admission. The patient was re-admitted to hospital under the care of Mr. Walton on January 10th, 1934, i.e. nineteen months later. *History.* During convalescence after the first operation he was said to have a swinging temperature, and experienced a distended feeling in the abdomen and had

diarrhoea. After a holiday he remained free from symptoms until one year ago. He then complained of attacks of upper abdominal pain, usually four to five hours after food. The pain lasted only a few minutes and was relieved by food. He had freedom from pain up to two months. *Four months ago* the same symptoms recurred, and he vomited on three isolated occasions. In addition he developed a hunger pain one and a half hours after food, and this was relieved by food and bismuth. He had gained two stone in weight, but his appetite was poor and he was troubled by flatulence. The attacks of pain now lasted two weeks, and he had remissions lasting nine weeks.

Physical examination. The patient was a well-built healthy-looking man. Abdomen—There was a slight tenderness under the tip of the right costal margin, and the upper rectus muscle was rigid. No other abnormal signs. *Test meal.* Free hydrochloric acid 0·2 per cent. Total acidity 75. *Barium meal.* The stomach was low and of moderate tone. There was a large ulcer niche on the lesser curve at the site of incisura angularis. Also spasmodic contraction of pyloric antrum. Duodenum normal. The appearances were those of a lesser curve gastric ulcer. A diagnosis of chronic gastric ulcer was made. *Operation.* A laparotomy was performed by Mr. Walton 19.1.34. There were adhesions between coils of intestine, and a large adherent ulcer was present on the lesser curve of the stomach. A partial gastrectomy was therefore performed. On opening the excised portion of stomach, there appeared a large ulcer the size of a shilling with a granulating edge.

Post-operative course. There was occasional pyrexia up to 99·8° F., but he was apyrexial and perfectly well on his discharge on 7.2.34, i. e. three weeks after the operation.

Pathological Report

Professor Turnbull concluded his descriptions of the naked-eye and micro-scopical appearances as follows :—

In this specimen it is difficult to decide whether the condition is chronic progressive peptic ulceration of a lymphogranuloma or a lymphogranulo-matous inflammation in the margins of a peptic ulcer. In either case the infiltration differs conspicuously from that usually found in chronic ulcers, and has the histological characteristics of a lymphogranuloma. The free cells are less uniform than in the previous two cases, and among them are a few giant cells such as are seen in Hodgkin's lymphogranuloma. The general picture is, however, not sufficiently characteristic of Hodgkin's lymphogranuloma for such a diagnosis to be made. The regional lymphatic glands show chronic inflammation, but, as in Case 1, they are not involved in the lymphogranulomatous change.

Acknowledgements

REFERENCES

Cheever, D., *Ann. Surg.*, Philad., 1932, xcvi. 911.

Coronini, C., *Beitr. z. Path. Anat. u. z. allg. Path.*, Jena, 1928, lxxx. 405.

Drope, H., *Virchows Arch. f. path. Anat.*, Berl., 1926, cclix. 147.

Freeman, L., *Colorado Med.*, 1928, xxv. 362.

Froboese, C., *Beitr. z. Path. Anat. u. z. allg. Path.*, Jena, 1927, lxxvii. 363.

Gunsett, A., and Oberling, C., *Bull. de l'Assoc. Franç. p. l'étude du cancer*, Paris, 1928, xvii. 385.

Harper, F. R., *Proc. Staff. Meet., Mayo Clinic*, Rochester, 1932, vii. 515.

Hayden, H. C., and Apfelbach, C. W., *Arch. Path. and Lab. Med.*, Chicago, 1927, iv. 743.

Holmes, G. W., Dresser, R., and Camp, J. D., *Radiology*, Minn., 1926, vii. 44.

Hunt, V. C., *Ann. Surg.*, Philad., 1932, xcvi. 210.

Junghagen, S., *Acta Radiol.*, N. York, 1927, viii. 339.

Kan, J. N., *Journ. Orient. Med.*, S. Manchuria, 1926, v. 9.

Klopstein, G., *Arch. f. Verdauungskr.*, Berl., 1933, liii. 40.

Knazelson, P., *Wien. Arch. f. inn. Med.*, Berl., 1924, vii. 117.

Mittelbach, M., *Centralbl. f. allg. Path.*, Jena, 1932, lv. 49.

Neubor, E., *Zentralorg. f. d. ges. Chir. u. ihre. Grenzgeb.*, Berl., 1925, xxxi. 309.

Pitt, G. N., *Trans. Path. Soc.*, Lond., 1889, xl. 80.

Ramond, F., Chêne, P., and Soulès, F., *Arch. d. Mal. del' app. digestif.*, Paris, 1930, xx. 680.

von Redwitz, E., *Zentralbl. f. Chir.*, Leipz., 1926, liii. 2087.

Reimann, S. P., *Cleveland Med. Journ.*, 1917, xvi. 94.

Ruggles, H. E., and Stone, R. S., *Calif. and West. Med.*, 1930, xxxiii. 486.

Ruppert, L. L., *Wien. Klin. Wchnschr.*, 1912, xxv. 1970.

Scott, E., and Foreman, F., *Ohio State Med. Journ.*, 1916, xii. 323.

Singer, H. A., *Trans. Chicago Path. Soc.*, 1931, 453–71.

Steindl, *Lancet*, Lond., 1925, ii. 720.

Sternberg, C., *Klin. Wchnschr.*, Berl., 1925, iv. 529.
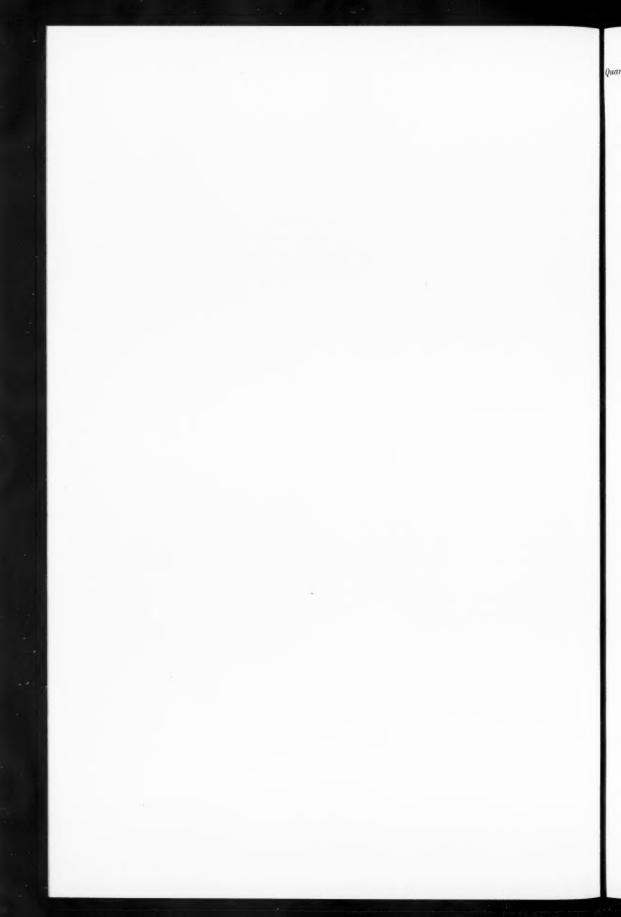
Sussig, L., *Pathologica*, Genoa, 1929, xxi. 397.

Tschilow, K., *Med. Klin.*, Berl., 1929, xxv. 1211.

Turnbull, H. M., *Proc. Roy. Soc. Med.*, Lond., 1929, xxiii. Sect. Med. 20.

Vasiliu, T., *Sang. Par.*, 1929, iii. 257.
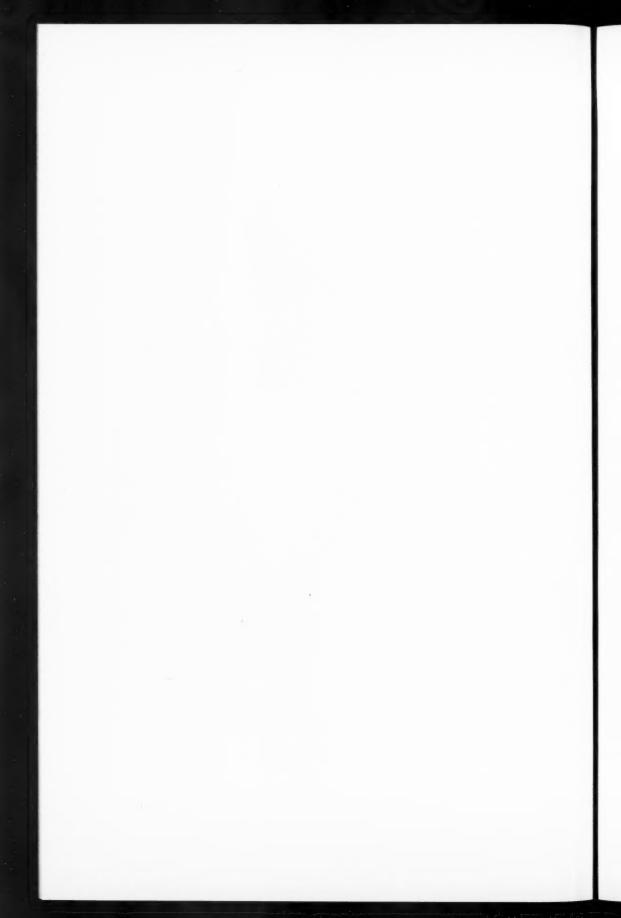
Walters, W., and Church, G. T., *Proc. Staff. Meet., Mayo Clinic*, Rochester, 1934, ix. 182.

Case 4. Barium meal showing ulcer on lesser curve of stomach near incisura angularis

93

OBESITY, HYPOGENITALISM, MENTAL RETARDATION, POLYDACTYLY, AND RETINAL PIGMENTATION:
THE LAURENCE–MOON–BIEDL SYNDROME [1]

By E. A. COCKAYNE, DAVID KRESTIN, AND ARNOLD SORSBY

With Plates 9 to 11

1. *Historical*

IN 1866, J. Z. Laurence and R. C. Moon reported the occurrence in the same family of four cases of retinitis pigmentosa associated with general imperfections. The patients were the offspring of healthy, non-consanguineous parents; the family consisted originally of ten children, but two had died in infancy, and of the eight surviving, four—the first, second, sixth, and seventh—were 'healthy in every respect', the remaining four being afflicted with visual defect and general disturbances.

The youngest, aged 7, the first to come under their notice, was a small,

'fat, flat-featured, heavy looking child . . . who instead of looking straight at an object, always looked to one side of it; and on being told to place her hand upon anything, she would be unable to direct it at once to the object, but felt about until she came in contact with it. . . . She appeared to see worse as evening approached. In daylight she was rather slow in her movements; but at night and by artificial light she walked with evident caution, always groping her way about with a degree of uncertainty. She also had a great objection to going out of doors at night, fearing that she should be " run over ".'

Ophthalmoscopically there were seen

'scattered over the fundus oculi, but especially aggregated towards its periphery . . . several irregular figures of a deep black colour. None were visible either in the situation of the macula lutea or its immediate neighbourhood. Their forms were exceedingly various, some being flakes or streaks of pigment, whilst others appeared as black oblong or oval spots, with fine dark lines extending from them, very closely resembling bone corpuscles in shape.

The pigment spots were apparently situated in the substance of the retina, on a level with its vessels—in some places interrupting these in their course, and at others running for a short distance closely by their sides. They were distinctly on a plane anterior to the choroid. The vessels of this latter structure could everywhere be most beautifully seen, even to the minutest ramification, excepting at those parts where the pigment obscured them from view. The spaces between the vessels were of a paler colour than the vessels themselves. Each optic papilla was of a reddish-pink colour, with a rather bright stippled centre; its margin softly defined, and surrounded by a narrow pale zone.'

[1] Received January 4, 1935.

      H

Apart from her small stature and her dull appearance, the girl was perfectly formed and well developed.

Of the three affected boys, the oldest, aged 20

'walks with a slouching heavy gait, as if he were tipsy. . . . He has a stolid heavy countenance, and appears to be rather obtuse and unintelligent. . . . He has always been observed to have defective sight. He sees very imperfectly in the daytime . . . and sees still worse by gas-light, and habitually feels and gropes his way about the house after dusk.

Ophthalmoscopic examination. . . . The superficial stratum of the choroid is considerably atrophied, allowing the choroidal vessels to be everywhere beautifully seen, with blackish, finely granular interspaces—which are probably the remains of the epithelial pigment layer. A few isolated dark black pigment spots are scattered over the fundi; none, however, being visible in the neighbourhood of either yellow spot, although the choroid at this part seems to be more atrophic, than at any other portion of the fundus.'

A younger brother, aged 18 and measuring only 4 feet 6½ inches in height, was a fattish heavy-looking boy. He too had a slouching gait, and also defective vision, especially after dusk. He had also slight nystagmus. The ophthalmoscopic appearances resembled those seen in his sister, only that the process was more advanced.

The youngest of the three affected brothers, aged 15, was also short, dull, and inanimate. His vision too was bad in daylight and still worse at night. The ophthalmoscopic appearances resembled those observed in his elder brother. His gait was less affected than that of his brothers. In the case of the boys in addition to the general underdevelopment,

'the organs of generation are also strikingly implicated. . . . The penis and scrotum of the eldest boy are not larger than those of an infant of twelve months old. Only the left testicle, and that an exceedingly small one, can be felt in the scrotum. In the second boy (Harry) the penis is somewhat larger, and two small testicles can be distinctly felt in the scrotum. There are a few fine scattered hairs on the pubes. In the third boy no testicles at all can be discovered, his penis and scrotum being about the same size as those of his brother Harry.'

In all the four cases, though the night blindness typical of retinitis pigmentosa was present, the fields of vision were full contrary to expectation.

Laurence and Moon recognized that the term retinitis pigmentosa did not fully satisfy the conditions present in their cases, and furthermore that the association with other defects was not accidental but the expression of a deeper underlying process:

'In calling these cases by the name of " Retinitis Pigmentosa " we have been guided rather by usage than by the intimate nature of the cases. Had we taken the latter view, we should rather have entitled our paper " Four cases of Arrest of Development and Atrophy of the Eye "; or we might have gone even a step further in the generalization of our title as the arrest of development was by no means confined to the eye, but affected several

other organs of the body.   In this later point of view, and more especially when we regard the general imperfection of the mental faculties, these patients may in a certain sense be not unaptly compared to cretins in a mild degree.   In no member of the entire family, however, was there any bronchocele.'

This bizarre combination of dwarfing, adiposity, hypogenitalism and mental retardation with retinal degeneration simulating retinitis pigmentosa, attracted no further attention till the beginning of the present century.   It contained too many elements that were new.   It was not till 1901 that Fröhlich described his syndrome of dystrophia adiposo-genitalis, whilst attempts to bring order into the chaos of conditions passing under the name of retinitis pigmentosa have yet to meet with success.   When Nettleship reviewed in 1908 the literature on retinitis pigmentosa he was impressed by the resemblance of the cases reported by Laurence with those reported in 1900 by Jonathan Hutchinson on notes made about twenty-five years earlier.   Though there were minor discrepancies in the two accounts, Nettleship, after discussing the cases with Hutchinson, was satisfied that they referred to the same family, Hutchinson having seen them about ten years after Laurence.   Hutchinson regarded the eye condition as due to 'disease of the choroids'; he, too, noted arrested sexual development and defective intellect.   He seems to have been more impressed by the presence of paraplegic symptoms than by the factors stressed by Laurence.

In foreign literature the cases are noted by Leber in his monumental review of diseases of the retina; he followed Nettleship in regarding them as cases of gyrate atrophy associated with general defects.   The fact that they constitute a syndrome was missed by him also.   This recognition did not come from ophthalmologists but from students of endocrinology, the stimulus being given by Fröhlich's description of hypophyseal adiposity with genital dystrophy.   Thus in 1908 Sievert described an incomplete Fröhlich syndrome in two out of eight surviving children, in whom there was present optic atrophy in addition to obesity.   The older child, a boy aged 15, had poor pigmentation in the periphery of the fundus, the younger, a girl aged 9, showed moderate atrophy of the periphery of the choroid with a few areas of retinal pigmentation, rather reminiscent of retinitis pigmentosa, a diagnosis gaining support from the presence of a mild degree of night blindness.   In 1912, von Jaksch reported a case of dystrophia adiposo-genitalis with mental defect, optic atrophy (held to be due to meningitis at the age of 3) and atypical retinitis pigmentosa (A. Elschnig)—atypical, for in addition to the characteristic changes of retinitis pigmentosa, there were also choroidal lesions around the disks.   Von Jaksch also reported that this patient had six fingers on the left hand, and that the fourth and fifth fingers of the right hand were dwarfed.   'Hypophyseal tumour with dystrophia adiposo-genitalis in two brothers' is the title of a communication a year later (1913) by Rozabel-Farnés.   In addition to the Fröhlich syndrome there were present polydactyly and visual disturbances,

blindness in one case, from optic atrophy which began at the age of 3, and in the second case bitemporal hemianopsia and atrophy of the temporal side of the nerve-head. Retinitis pigmentosa does not appear to have been present. In the same year Bertelotti described a case of Fröhlich's syndrome associated with mental deficiency, non-consecutive atrophy of the disks, retinitis pigmentosa and polydactyly on the right hand and both feet. Measurable dwarfing, absolute and relative, of practically the whole skeletal structure is also noted. Bertelotti recalls the cases of Rozabel-Farnés and holds that the Fröhlich syndrome with polydactyly constituted a distinct syndrome, and, as the lesions are congenital, they are probably caused by a teratoma of the pituitary and not by an acquired new formation as Fröhlich believed. Thus whilst Rozabel-Farnés and Bertelotti and also von Jaksch were drawing attention to poly-dactylism and mental deficiency as an association of Fröhlich's syndrome, Sievert and von Jaksch had noted atypical retinitis pigmentosa and mental deficiency as associated lesions. These later associations were also observed by Madigan and Moore in 1918.

The association of the Fröhlich syndrome, with atypical retinitis pig-mentosa and mental deficiency on the one hand, and polydactyly and mental deficiency on the other hand, makes an interesting connecting link in older observations on the association of polydactylism with retinitis pig-mentosa. These cases are indeed few in number. They had been reported by Höring (1864), Stör (1864), de Wecker (1865), Wider (1885), Siegheim, Darrier (1887), Herrlinger (1889), and in two brothers by Grossman (1908). It is of interest to note that in all but Darrier's case, and in one of Grossman's cases, mental changes are recorded.

That dystrophia adiposo-genitalis, retinitis pigmentosa, and polydactyly constitute a unit syndrome was clearly recognized by Bardet in recording an isolated case of this association in 1920. He failed to appreciate mental deficiency and familial occurrence as an essential factor of the syndrome. Two years later, Biedl in showing two cases occurring in the same family expanded the syndrome to include : ' Congenital malformations (Atresia ani, polydactylism, retinitis pigmentosa, deformities of skull) ; retarded mental development, marked obesity with or without genital hypoplasia and peculiar disturbances of digestion. No changes in the pituitary gland, no signs of cerebral tumour or increased intracranial tension.' Diabetes is mentioned as a concomitant symptom. Raab, who reported Biedl's cases in full, speaks of the syndrome as consisting of retinitis pigmentosa, poly-dactylism, adiposity, genital hypoplasia, and mental deficiency. Solis-Cohen and Weiss in 1925, in reporting the occurrence of four cases in one family, drew attention to the description by Laurence and Moon—(Hansell, who described the fundi, in discussing these cases briefly in 1924 had done likewise. *Ophthal. Soc. U.K.*, vol. 44, pp. 303–8, 1924). At the suggestion of Solis-Cohen and Weiss the condition is now generally known as the Laurence-Biedl Syndrome. It might with equal justice be named the

Laurence-Bardet Syndrome. To attach the names of Laurence and Moon only would perhaps be the most desirable course.

It is of interest to note that the full syndrome, including its familial nature was well described by Gordon in 1907. He missed its significance and recorded two cases, a brother and sister aged 9 and 14 years respectively, showing mental dullness, polydactyly, obesity (and in the case of the boy, also hypogenitalism), associated with markedly defective vision, as cases of late Tay-Sachs disease. This diagnosis was presumably made on the fundus findings; in the case of the boy there was: ' a large irregularly outlined patch of choroidal pigment in each not symmetrically placed. Choroidal vessels too evident in all parts of the fundus. Partial atrophy of optic nerves and retinae.' In the case of the girl ' the optic nerves and retinae were atrophied; oval area, including the fovea and about the size of the papilla much redder than the remainder of the fundus' (H. F. Hansell). In passing, it may be noted that such recent works as the *Kurzes Handbuch der Ophthalmologie* and Waardenburg's *Das menschliche Auge und seine Erbanlagen* still record these cases as unusual cases of Tay-Sachs disease. Junius draws upon them in an even more recent article (*Ztschr. f. Augenheilk.* 1932, lxxvi, 225).

Nine years earlier, in 1898, de Cyon seems to have observed a family group of three brothers exhibiting this syndrome. He is reported only in abstract. One of his cases is described as fat, mentally dull, and as having polydactyly and visual disturbances (' slight ptosis, miosis, nystagmus '; nothing is said of the fundus). Two brothers were likewise affected but ' to a different degree '.

Grossman's description in 1908 of two brothers with retinitis pigmentosa and polydactyly, and the fuller account of one of them describing hypogenitalism, mental deficiency, and congenital morbus cordis, obviously refers to two cases of this syndrome. To Grossman the point of interest was the association of congenital heart disease with other congenital defects.

2. *Review of Literature* [2]

During the past ten years about thirty isolated cases have been reported in addition to fifteen familial groups. The collective evidence of these reports is of some interest.

A. *Analysis of thirty isolated cases of the Laurence-Moon syndrome.* 1. *Antecedents.* Practically all reports refer to the parents as healthy. In no case did either of the parents or other ascendants exhibit the syndrome. Syphilis in the parents is mentioned twice (Orgaz, Bailliart, and Schiff-Wertheimer, first case), but a larger number of the reports are negative in this sense. Consanguinity in the parents is reported by Bauer

[2] Four cases were overlooked in this analysis three (two boys and one girl) coming from a family reported by J. H. Hutton, *Clinical Medical, and Surgery* 39 ; 574, 1932, and the fourth being an isolated case, a boy reported by L. Dods, *Medical Journal of Australia*, 21, ii ; 277, 1934. Hutton's cases show the complete syndrome except that mental development does not seem to have been greatly affected. There was no consanguinity of parents and there were no normal sibs. Dods's case is briefly reported as a case showing the Fröhlich syndrome in association with retinitis pigmentosa ; nothing is said about polydactyly or mental development.

(first case), Lange (first case), Rieger and Trauner, Orgaz and Ritter. That there was no consanguinity is noted by Denzler, McAlpine, Boenheim (first case), McKinney, and Wuite. Other reports say nothing on this head.

The family history is generally negative in the reported cases, but observations on obesity, psychic disturbances, and polydactyly are given in some.

Biedl and Raab (third case) observed obesity in the parents. Deusch reports it as a frequent occurrence in the father's family. In Griffiths' case the mother was plump, ' a tendency which runs in the family ', whilst Wuite reports that two sisters of the paternal grandfather were abnormally fat, one of them being also very small.

Sterling's patient came from ' highly degenerated stock '. Alcoholism in the father is noted by Borchardt. In Deusch's case the father was a drunkard and a maternal uncle mentally unsound. Lange too (first case) reports a father who was a drunkard ; an uncle who was an epileptic ; and on the maternal side, an aunt who was dumb and mentally defective ; more remotely there was epilepsy on the mother's side. Epilepsy in the paternal grandfather is reported by Wuite. In McCrae's case the father ' gave the impression of being rather below the average in mental powers ' ; he ultimately committed suicide.

Six fingers on each hand in a paternal uncle (Deusch), in a maternal uncle (Lisser), and double thumbs on one hand in a maternal uncle (Griffiths) have been observed.

2. *Sibship.* A striking feature is the history in the majority of cases of suggestive lesions in deceased members of the family.

Polydactyly amongst deceased members of the family is mentioned by Deusch, Bauer (first case), Lange (first case), Rieger and Trauner, Lisser, McKinney, Griffiths, Orgaz, and Borchardt. Poos, who gives no other details on the family, states that a sister of the patient is blind and has six toes. Spina bifida in a sister who had died at 3 months is noted by Denzler. The cases reported by Borchardt and by Rowe probably had affected sibs who were not examined.

Of special interest are the cases of Griffiths and of Orgaz. Griffiths' patient who showed syndactyly in addition to polydactyly, had two sisters with webbed toes, though otherwise normal. Orgaz's patient had two younger brothers with polydactyly but who were apparently normal otherwise. In neither of these families was the deformity noted in ascendants.

For a further analysis of the family relationship see Table (pp. 116–18).

3. *The syndrome.* (a) *Obesity* is a constant feature. Practically all writers state that the patient was fat from infancy, the obesity becoming more marked with time. Only occasionally does obesity seem to have developed after some illness in early life. In Lange's case it came on after the age of $1\frac{1}{2}$ years.

(b) *Hypogenitalism* is not always present, nor easily determined when present, particularly in the case of girls before puberty. In McAlpine's case hypogenitalism was slight ; in Serejski's and Rowe's cases it was not present at all. In Denzler's case it was slight in a boy aged 12 ; the same patient seen ten years later by Willi had fully developed genitalia.

(c) *Mental retardation* is present in the great majority of cases, ranging from mental deficiency to idiocy. A normal mentality is recorded by Rieger and Trauner. Only mild disturbance, not amounting to definite

mental deficiency was present in Biedl and Raab's patient. Bailliart and Schiff-Wertheimer (first case) say nothing about their patient's mental state; their second case had only mild disturbance.

(d) *Polydactyly* was absent in the cases of Biedl and Raab, Deusch, Zondek, and Sterling. Six digits on both the hands and feet were observed in the cases of Bailliart and Schiff-Wertheimer (both cases), Boenheim (first case), Turner, Poos, and Ritter. Syndactyly of toes without polydactyly was present in the cases of Lange (third case), Deusch, and Sterling, whilst both the defects were present in three cases (Griffiths, Turner, and Ritter). Turner's case in addition also showed incomplete doubling of thumbs.

(e) *Retinal degeneration* is reported by all observers, apart from Turner. Generally visual defect is noted in early childhood, but in quite a number of cases it does not become apparent till later. In Rowe's case it was not observed till the age of 5, and in McAlpine's till 8. Nystagmus is almost invariably present.

4. *Associated conditions*. Microcephaly is reported by Bardet; mild oxycephaly by Biedl and Raab, Serejski, and by Turner; brachycephaly by Rieger and Trauner. Genu valgum was observed by Rieger and Trauner and by Turner. Turner's case also showed dislocation of both patellae. Kyphoscoliosis is reported by Serejski. Pott's disease of the dorsal spine occurred in Bardet's case at 11.

Congenital heart disease was observed by Wuite. It is of interest to note that in the family of Deusch's case an infant with six fingers on both hands had died from congenital heart disease.

Head nodding is reported by Deusch, and choreiform movements by McKinney and by Wuite.

Muscular weakness was observed by Rieger and Trauner.

In most cases stature is dwarfed. Griffiths and Lange report stature rather higher than normal for the age of their patients.

B. *Analysis of seventeen familial groups* (including the cases by Laurence and Moon and by Biedl and Raab). 1. *Antecedents*. As in the isolated cases, the syndrome was never observed in either of the parents or in ascendants. Consanguinity is reported in four groups (Ricaldoni and Isola, Willi and Clay (a and b). The absence of consanguinity was noted in seven groups (Laurence and Moon, Solis-Cohen and Weiss, Bernhardt, Beck, Boenheim, Ornsteen, Reilly and Lisser). Alcoholism in the parents was noted twice (Feeder, Willi). In no case was there evidence of syphilis in the parents; negative Wassermann reactions in both parents are reported by Solis-Cohen and Weiss, and by Ricaldoni and Isola.

Obesity was noted twice in the ascendants of the father (Ricaldoni and Isola, Ornsteen). Pathological obesity in the mother was noted by Feeder. In Willi's group the mother and aunt were very fat. Excessive overweight (but no mental deficiency) is noted in the paternal ascendants by Ornsteen.

Psychic disturbances. 'Much mental trouble' in the family is reported by Looft. In Willi's group a maternal aunt was mentally defective; there was also obesity and alcoholism in other ascendants on the mother's side. Insanity in a brother of the grandfather is reported by Bernhardt.

Polydactyly is not reported in the antecedents by any observer.

A history of blindness in several remote ascendants is reported by Ricaldoni and Isola.

2. *Sibship.* As in the isolated cases suggestive lesions in deceased members of the family are a striking feature.

Polydactyly in deceased members is noted by Biedl and Raab, Looft, Feeder, Ricaldoni and Isola. In the latter family imperforate anus occurred in an infant who died at 7 days and had no polydactyly.

Of special interest from the genetic aspect is the family group reported by Clay. The syndrome was present in two out of three children, the offspring of parents who were second cousins; and it was also present in a cousin of the affected children. This child, who had four normal sibs, was also the offspring of consanguineous parents.

For a fuller analysis of the family relationships see Table (pp. 116–18).

3. *The syndrome.* (a) *The complete syndrome.* This was observed in both members of a group of two by Bing, Biedl and Raab, Beck, Herzog, Feeder and Friedmann: and in all the members of a group of four by Ricaldoni and Isola. The complete syndrome was also noted in one out of two cases by Looft and by Clay (a), and in two out of four by Solis-Cohen and Weiss; in three of the four cases in which it was incomplete, the missing feature was polydactyly; in the fourth (Clay (a)) there was no definite hypogenitalism.

(b) *The incomplete syndrome.* Apart from incompleteness by the absence of polydactyly in the three cases just mentioned, the syndrome was incomplete in other cases from the same cause. Thus polydactyly was absent in the cases of Laurence and Moon, Ornsteen, Reilly and Lisser, Willi, and Clay (b) (in Willi's group webbing of fingers and toes, and in Clay's (b) syndactylism of toes only was present). In Bernhardt's two cases and in Clay's (b) the mentality was hardly affected; only mild mental deficiency was present in one of Ornsteen's cases. In Willi's cases too, the mentality was not much affected; one of the two was hardly below normal and the other was just below average. Hypogenitalism was only doubtfully present in one of the cases of Reilly and Lisser (a girl of 13); it was absent as already noted in a case of Clay (a).

4. *Associated conditions.* Skull deformities do not seem to have been observed in the familial cases.

That the hands and feet are short is observed by Beck and by Ornsteen, the former also noting malformation and irregular toes, and the latter flat-foot; 'pudgy' fingers and toes are reported by Clay (b). Genu valgum is mentioned by a number of observers (Biedl and Raab, Solis-Cohen and Weiss, Ricaldoni and Isola, Beck). In one of Willi's cases congenital bilateral coxa vara was present. Dorsal scoliosis in one case is reported by Ricaldoni and Isola, and kyphosis in two affected sisters is noted by Reilly and Lisser.

A (?) functional murmur was observed in one case by Ricaldoni and Isola. Cases of frank congenital heart disease do not seem to have been observed in the familial groups.

Involuntary movements: apart from the almost constantly present nystagmus, none are reported.

Psoriasis in a brother and keratosis follicularis in a sister are reported (Friedmann).

Shortness of stature is reported in two cases by Solis-Cohen and Weiss. This was also observed by Laurence and Moon.

(c) *Anomalous cases.* Some of the isolated cases reported as being examples of the Laurence-Moon-Biedl syndrome are not so much anomalous, as of doubtful diagnosis. To this group belong those reported by Ratner, Zondek (first case), Borchardt (second and third case), the two brothers reported by Boenheim and the third and fourth case of Reilly and Lisser.

Of greater significance are the cases of Turner and of Weiss. In Turner's case the fundi are said to have been normal; nothing is said of the state of vision. Weiss reports two sisters who showed obesity, genital dystrophy, and mental deficiency. There were no eye changes and no polydactyly, but both patients had nerve-deafness. Weiss regards the nerve-deafness as replacing the retinal degeneration.

3. *Case Records* [3]

The A. *family.* Both parents were English; they were healthy, and showed no physical or mental defects. They were not blood relations, and to the best of their knowledge were of healthy stock. There were no miscarriages. Three girls and seven boys were born and all reared, but for one boy who died at the age of two; he had six fingers on each hand. All the pregnancies and births were uneventful. The patients were the oldest girl, Martha, the second oldest boy, Edward, and the youngest but one, Alfred. The other children ranging from 23 to 5 years of age were all in good health, useful members of the community, and none of them showed any obvious defects. The oldest son only was married and had one normal child.

Martha, aged 26, unmarried, was considered to be normal at birth. Development during infancy and childhood was normal; she was generally considered 'plump' but not excessively obese. At school she was very backward and left at 14 years, two or three standards below the average. At 15 years it was first noticed that her vision was defective, and this became rapidly worse so that she could not pick out individual letters or see objects at a greater distance than a few feet. No difference was experienced during night and day. She has done no work since leaving school and had kept fairly well, except for occasional vague pains in the muscles of the shoulders and back. There have been no headaches. The weight had remained fairly constant during the last four or five years. The catamenia commenced at 12 years of age; they were rather excessive at the beginning and have been regular ever since.

Examination. Weight 11 st. 5 lb. Height 5 ft. 2½ in. A placid, agreeable healthy-looking young woman of ruddy complexion and a rather blank, vacant look. The intelligence was roughly that of a girl of 9 or 10. She was co-operative, answered simple questions readily. She was moderately stout, particularly well covered about the bust, hips, and thighs. Breasts were well developed and non-lactating. The head was brachycephalic, skin was smooth and of fine texture with abundant, fine, downy hair on the limbs; abundant axillary and pubic hair, the latter of feminine distribution. The hands were short and fingers straight, well shaped, but not tapering; the palate high, narrow, and arched; teeth crowded and carious; tonsils red,

[3] The cases described, with the exception of the first patient in the second group, were demonstrated at the Ophthalmological Section of the Royal Society of Medicine (T. R. Hill and A. Sorsby).

cryptic, and unhealthy. *Ophthalmic examination.* Pupils widely dilated, equal, reacting briskly to light but poorly to accommodation; no paresis of the ocular muscles. Fine, irregular, rapid nystagmus of the pendulum type most obvious on lateral movement of the eyeball. Vision with correction (R. – 2·5 D. Sph., L. – 1·0 D. Sph.) was less than 6/60. Media : clear. Fundi : Typical retinitis pigmentosa—typical in the form and distribution of the pigment, in the colour of the disks and narrowing of the blood-vessels. The pigmentary disturbance was largely equatorial and rather disproportionately small to the high degree of optic atrophy. Hearing good ; motor and sensory functions of other cranial nerves normal. The upper limbs possessed good motor power, but both exhibited hypotonus, especially of the wrists and fingers; there was also moderate inco-ordination and dysdiadokokinesis. The muscular power in the limbs was good. Ataxia was not present. All deep reflexes of arms and legs, brisk ; plantar reflexes gave a flexor response. Sense of touch, pain, heat, and cold, and of position, all good.

The cardiovascular system revealed nothing abnormal. Blood-pressure was 135 systolic and 90 diastolic. Examination of lungs and abdomen revealed nothing abnormal. No skeletal or skin abnormalities.

Urine	clear
Blood Wassermann reaction . .	negative
Blood urea	19 mg. per cent.
Blood-sugar	Fasting level 0·034 per cent.
After 50 grm. of glucose . .	½ hour 0·168 per cent.
,, ,, . .	1 hour 0·125 per cent.
,, ,, . .	1½ hours 0·075 per cent.
Blood-grouping . . .	Moss III
Radiograph of skull . . .	Normal sella ; normal conformation ; sutures united ; sinuses clear.

Edward, aged 22, unmarried, was healthy at birth and appeared to develop normally until he attended school where he was considered backward. Nothing abnormal was noticed with vision until about 9 years of age when definite impairment was observed at school. Since then has been able to see and distinguish objects and find his way about during the day, but has experienced great difficulty at night when he sometimes stumbles in the dark. He can see and distinguish letters of large type but has never learnt the letters of the alphabet. There has been no obvious change in his vision during the last ten or twelve years. He felt quite fit and considered himself healthy apart from his vision. Except for a fall on the head at 2 years of age there was nothing of note in the past history.

Examination. Weight 13 stone 11 lb., height 5 ft. 4 in. A large obese lad with a completely vacant, unintelligent, and uninterested expression. Oblong-shaped head with square forehead, narrow high palatal arch, teeth carious but not crowded, tongue small and smooth. Obesity, especially over the arms, breasts, abdomen, and thighs giving the body a smooth well-rounded contour and producing a distinctly feminine build. The hands and feet were comparatively small, the fingers delicately shaped and somewhat tapering. The arms and legs were covered with fine, sparsely scattered hairs, and the face and chin by a soft down which he shaved once in two or three weeks. The penis was small and corresponded to that of a boy of 13. Both testicles were of normal size and in the scrotum. Pubic hair was

plentiful and arranged with a horizontal upper level suggesting a feminine distribution.

Both pupils were equal, of medium size and slightly eccentric. Constant bilateral regular lateral nystagmus of slow rate present in all positions, but increased on lateral fixation, more marked to the right. Vision with correction (− 2·0 D. Sph. each eye) less than 6/60 each eye. Media clear. Fundi similar to his sister's, but there was more atrophy and less pigmentary disturbance. No facial paresis, hearing good. Muscle tone and power in the limbs good. No definite inco-ordination detected. No tremors were present, deep reflexes in upper and lower extremities brisk. Abdominal reflexes all brisk. Plantar reflexes both gave flexor response. Sensation to cotton wool, pin-prick, heat, and cold, and position all apparently good. Examination of the heart, lungs, and abdomen revealed nothing abnormal. The blood-pressure was 140 systolic, 85 diastolic. No skeletal or skin abnormalities.

Urine	clear
Blood Wassermann reaction .	negative
Blood urea	25 mg. per cent.
Blood-sugar	Fasting level : 0·063 per cent.
After 50 grm. of glucose . .	½ hour 0·069 per cent.
,, ,, . .	1 hour 0·131 per cent.
,, ,, . .	1½ hours 0·063 per cent.
Blood-grouping	Moss IV
Radiograph of skull . . .	General conformation and sella normal ; sutures united ; sinuses clear.

Alfred, aged 16, was healthy at birth, except for a supernumerary digit on each hand which was removed in early childhood. He developed normally up to four years ago. At this time vision was found to be impaired, and this has always been most noticeable at night. Glasses were ordered with which he was able to see better. He had been backward at school, and since the age of 10 had been to a special school for mentally defectives where he had been taught cabinet making. He was able to make simple models. For some years had complained of frontal headache, but otherwise had always felt quite well. There was nothing of note in the previous history, except for the removal of the supernumerary digits in infancy.

Examination. A normally formed lad with a masculine build. Weight 8 st. 10 lb., height 5 ft. 4 in. There was no excess of adipose tissue in the region of the breasts, thighs, or abdomen. Hair was present on the face and chin, in the axillae, and at the pubes in normal amount, and masculine distribution. Penis normally developed for his age, both testes in scrotum. Teeth healthy ; tonsils enlarged and septic looking.

Over the ulnar aspect of the left hand at the level of the metacarpo-phalangeal joint there was a small linear scar 1 cm. long, and over the corresponding site of the right hand a linear scar 3 cm. long. Beneath the latter was a slight bony projection.

Vision with correction (R.−4·0 D. Sph., L.−2·0 D. Sph.) was less than 6/60. Media clear. Fundi as in his brother. Pupils reacted well to light and accommodation. There was no nystagmus. Hearing good. Other cranial nerves normal. Tremors absent. Co-ordination of hands and legs good. No ataxy. There was some degree of hypotonicity in both upper and lower extremities, but muscle power was good. All deep reflexes in

upper and lower extremities brisk. Abdominal reflexes brisk. **Plantar** reflexes both gave a flexor response. Sensation to pin-prick, cotton wool, heat, and cold, and position apparently normal.

The cardiovascular and respiratory systems presented no abnormalities. Blood-pressure: 138 systolic, 80 diastolic. Abdomen showed no abnormality.

Urine	.	clear
Blood Wassermann reaction	.	negative
Blood urea	.	26 mg. per cent.
Blood-sugar	.	Fasting level 0·051 per cent.
After 50 grm. of glucose .	.	½ hour 0·106 per cent.
,, ,, .	.	1 hour 0·097 per cent.
,, ,, .	.	1½ hours 0·092 per cent.
Blood-grouping . . .	.	Moss III
Radiograph of skull . .	.	Normal conformation and sella; sutures united; sinuses clear.

Report on Mental Condition of these Three Patients (Dr. A. C. Williams)

They are all rightly to be called feeble-minded. In all cases the defect was rather more of the type that is usually associated with cerebral lesions than with primary amentia. The educational attainments, and especially the reading power of all of them, was very slight, but this is partly due to lack of vision and to disturbances of health. (Martha had early and excessive catamenia and Alfred has severe headaches.) The intrinsic intelligence, making full allowance for other factors, is quite definitely at the level of the mentally defective.

Edward has a mental age of about 9, Martha of about 10, and Alfred of about 8½ years.

Alfred was lately at a special (M.D.) school. The other two, who are older and a little better, attended a little Church school, but have been unable to carry out any occupation.

The B. *family.*[4] The presence of defective vision, obesity or supernumerary digits was unknown in either parent, grandparent, or great-grandparent. The parents were English and unrelated. A history of mental instability was obtained on the paternal side: the grandfather had attempted suicide, and an uncle was still alive in a mental home to which he was removed after also attempting suicide. The father had never exhibited any mental defect, but was considered to possess poor physique and died of pneumonia four years ago at the age of 35. The mother was alive and in good health but was rather irritable and highly strung. She had had no illness or miscarriages, three children were born alive and these were the subject of investigation. A fourth—the mother's last pregnancy—was stillborn (breech presentation). According to her statement this child showed no polydactyly.

Complete examination of the mother was not possible but she appeared to be of normal physical development. The blood Wassermann reaction was negative. Her fundi were not examined.

Adrian. (Examined by the courtesy of Dr. S. Langton, Medical Superintendent, Royal Earlswood Institution.) The eldest of the three, aged 15, was a healthy baby at birth except that he was born with an extra

---

[4] These cases are briefly noted by Julia Bell (*a*) in an article on Polydactylism.

digit on the left hand and on both feet. He was considered a rather fat baby, and came to be regarded early as mentally defective. He walked and could talk at 18 months to 2 years, though he could only 'say a few words'. When about 4 years of age it was noticed that his vision was impaired, and this was more obvious at night. Soon after his mental development appeared very retarded, and both visual and mental defects seemed to get very much worse with the progress of time. Though not regarded as a cretin, he received thyroid for some months at the Hospital for Sick Children, Great Ormond Street, but without effect. In May 1930 he was admitted to the Royal Earlswood Institution. In November 1931 he had a sudden attack of almost complete blindness and has been unable to see more than light since then.

Examination. He was mentally dull and physically a rather big, well covered lad, yet not grossly obese. The thighs and upper arms were well rounded off, the chest rather flat, but the abdomen a little protuberant. The skin was soft and smooth. The hands were small with slightly tapering fingers. The chin was covered with a very fine soft down, and a few sparse hairs were present immediately over the pubes. The penis was small and undeveloped. Both testicles seemed to be of normal size for a lad of 15 years, and were in the scrotum. He was quiet, unable to see individuals and was able to answer very simple questions. He co-operated to the extent of carrying out simple, common requests, such as putting out his tongue and gripping hands. More complex manœuvres could not be carried out.

The pupils were equal in size and reacted sluggishly to light and to accommodation. There was no ocular or facial paresis. A fine rapid nystagmus was elicited on lateral movement to either side. The muscle tone of the limbs was very poor, but no obvious muscle weakness was observed. Co-ordination good. Arm-jerks, knee- and ankle-jerks were easily obtained and the plantar response was flexor. Sensation seemed unimpaired. More detailed examination of the nervous system was not possible. The cardiovascular and respiratory systems showed no obvious abnormalities.

X-ray of the skull showed a normal pituitary fossa. Urine was clear. The blood Wassermann reaction was negative.

Fundi. There was advanced simple ('primary') optic atrophy. The vessels were narrow. The maculae were markedly stippled and the periphery showed but little departure from the normal, apart from a few discrete dots of pigment not definitely related to the blood-vessels.

Feet. Six completely separated toes, symmetrical on each side. X-ray showed a broad fifth metatarsal (fused double bone).

Hands. There is a scar on the ulnar side of the hypotenar eminence, at the site where an extra finger was removed from left hand (it had three phalanges and was smaller than the fifth finger). X-ray showed a probably normal fifth metacarpal of the right hand, whilst the fifth metacarpal of the left was distinctly broad.

Cynthia, aged 12, was born after difficult labour and weighed 10½ lb. There were six fingers on each hand and six toes on each foot, but otherwise she seemed a healthy child and of normal development. Progress after birth was good and she walked and talked at 12 months. Further development seemed satisfactory up to about 5 years when she became very dull and found it difficult to learn anything at all. At that time it was found that she had some difficulty in finding her way about in the dark and she complained

greatly of headaches. Since then she had remained very backward and had had to go to a special school. Her habits, however, had been clean and there had never been nocturnal enuresis.

Examination. A well-developed girl, a little fat round the neck and chin. A small linear scar on the ulnar side of each hand was present where a supernumerary digit was removed as a baby. X-ray showed that the fifth metacarpals were broad (? fused double bone). Each foot had fully developed six toes; the bases of the fifth and sixth metatarsals were fused. She seemed quiet and placid with a slow mental response. Visual acuity with correction (R. + 4·0 D. Sph. + 1·0 D. Cyl. axis 90, L. + 5·0 D. Sph.) = ? 6/60 each eye.

The ocular movements were full, no nystagmus was present, other cranial nerves were unaffected. The visual fields could not be determined. Muscle power and tone good. All deep reflexes brisk. Abdominal reflexes present. Plantar responses, flexor.

No inco-ordination, ataxy or sensory changes detected.

The cardiovascular and respiratory systems were normal. Blood-pressure was 110 systolic and 65 diastolic.

X-ray of skull showed normal sella. The abdomen was of good shape; neither liver nor spleen felt.

Fundi. As a first impression the fundus appeared normal: more minute examination revealed a definitely stippled maculae, heightened in colour.

In the periphery the choroidal vessels were easily seen. Optic disks normal.

The Wassermann reaction of the blood was weakly positive. The Kahn reaction was + − −. Cerebrospinal fluid was not under tension, clear, and showed one cell per cm. Total protein 0·02 per cent. No excess of globulin. Wassermann reaction and Kahn reaction of cerebrospinal fluid negative. Lange 0011000000.

The *Psychologist* (Miss Bowley) reported that the child was slow, languid, and dreamy. Mental response was very slow and required much effort, her attention could not be held for long.

Burt revision test: chronological age 12·6, mental age 6·2, giving an intelligence quotient of 0·49

Drawing of a man: 5·3 years.

The child ranked as a high grade imbecile who could not state the number of fingers on each hand, copy a diamond, name the days of the week or repeat digits backwards. Serious mental retardation was present.

Sheila. Aged 8, was born after a normal and uneventful delivery. She was breast-fed and progress appeared normal up to the age of 5 years, Teething was normal and she walked and talked at 12 months.

During the past three years she had been becoming increasingly backward. Her mother complained that she had been increasingly irritable, nervy, and bad tempered. Always appeared dull and had never been able to learn. Occasionally complained of right-sided headache and sleepiness. At birth she had been unusually plump and had remained abnormally fat since. She was born with six fingers on each hand, the extra digits being removed in childhood. The feet were normal. Since about 4 years of age, the child seemed to grope about when looking for things at night.

Examination. The child was definitely obese, the adiposity being most noticeable over the neck, chest, and abdomen. Her hands were rather

small and the fingers tapering. Over the ulnar aspect of each hand was a small linear scar where a supernumerary digit had been removed.

The child appeared dull, somewhat apathetic, and looked vacant. She answered 'yes' to all questions, did not know the alphabet, and called all coins a penny. Visual acuity: with correction (R. and L. + 3·0 D. Sph.) = ? 6/60 each eye. Visual fields could not be investigated owing to insufficient co-operation. There was a fine horizontal pendulum nystagmus of moderate rate on lateral fixation to the right; otherwise cranial nerves appeared normal.

Muscle tone and power in the limbs was good. There was no inco-ordination or ataxy. No ankle clonus. Abdominal reflexes and all deep reflexes brisk. Plantar responses flexor. Sensation apparently normal. Cardiovascular and respiratory systems normal. Blood-pressure: 100 systolic, 80 diastolic. Examination of the abdomen revealed no abnormality. Blood Wassermann and Kahn reactions: negative. Cerebrospinal fluid clear, not under excessive tension, 2 cells per cm. Total protein 0·02 per cent. No excess of globulin. Wassermann reaction and Kahn reaction negative. Lange 0011000000.

Blood-sugar. Fasting 0·093 per cent. ½ hour after 50 grm. of glucose 0·143 per cent., 1 hour 0·150 per cent., and 1½ hours 0·112 per cent. No sugar or other abnormality was present in the urine. X-ray of skull showed no abnormality.

Fundi: as in her sister Cynthia.

Psychologist's report (Miss Bowley). Child appeared tired, slow, and apathetic.

Burt revision test: chronological age 7·11, mental age 4·8, giving an intelligence quotient of 0·59.

Drawing of a man: 4½ years.

Ranks as a low grade moron. Serious retardation accompanied by physical languor and lack of animation is well marked.

4. *Discussion*

(a) *Retinal degeneration*, in one form or another, is present in all the recorded cases with the doubtful exception of Turner's case.

Our own cases showed strikingly different pictures in the two families One family showed fairly typical retinitis pigmentosa, with its characteristic 'bone corpuscle' pigment along the retinal vessels towards the periphery; the other showed the appearances typical of cerebro-macular dystrophy— stippled maculae (and optic atrophy in the eldest), together with some mild atrophy of the peripheral part of retina as shown by the visibility of the choroidal circulation and some fine pigmentary disturbance. The original cases of Laurence and Moon were regarded by Nettleship as gyrate atrophy, and the subsequent cases show a variety of pigmentary disturbances, ranging from typical retinitis pigmentosa to almost every conceivable form of atypical pigmentary disturbance.

Typical retinitis pigmentosa is recorded amongst others by Raab, Ricaldoni, and Isola, Willi, and by Bailliart and Schiff-Wertheimer. 'Atypical retinitis pigmentosa' is noted by Solis-Cohen and Weiss, Lisser,

Rieger and Trauner, Beck, and by Sterling amongst others. The atypical forms range from small chorioretinal lesions (Beck, Solis-Cohen, and Weiss) to marked chorioretinal atrophy (Clay); from peripheral pigmentary lesions sparing the macula (most observers) to a lesion involving the macula (Rieger and Trauner and Bernhardt); from retinitis pigmentosa sine pigmento (Sterling, Lange), to atypical retinitis punctata albescens (Lisser). Typical retinitis pigmentosa would appear to be the exception, and only mild retinal degeneration is reported by McKinley.

Pigmentary disturbance of the retina, which sometimes takes the form of retinitis pigmentosa, is thus the fundus appearance characteristic of the Laurence-Moon-Biedl Syndrome. Apart from ophthalmoscopic appearances, the eye symptoms differ in one important respect from typical retinitis pigmentosa: the juvenile onset of a severe fundus lesion is uncommon in classical retinitis pigmentosa.

In this connexion Wibaut's attempt to differentiate two types of retinitis pigmentosa may be noted. From an analysis of the pedigrees collected by Bell he argues that the type inherited in a dominant manner is a clinical entity distinct from the recessively inherited variety. The one has no associated lesions, whilst the other has: in 300 cases inherited dominantly there was only one case showing cerebral complication, whilst the cases of recessive inheritances were prone to deafness and other lesions of the central nervous systems.

(b) *Polydactyly* is a defect which is widely spread throughout the animal kingdom. In man it may be present in all the four or in one or more extremities. In some families syndactyly is associated with it. The affection may be symmetrical or asymmetrical and the type and situation of the affection may vary from individual to individual in the same family.

In situation, the post-axial position (towards little finger or toe) is commonest; but pre-axial and central varieties are also known.

In degree, three varieties are recognized. (a) Small, fibrous skin-clad nodules, with or without a bony centre; (β) bifurcation of normal digits with complete or partial duplication of the part. The bifurcation may be of any extent, originating either at the distal, middle, or proximal end of either of the digital bones, or at either end of the joints. In the full form there is complete duplication of the digit as far as the carpus or tarsus; (γ) irregular and intermediate forms, e.g. attachment of digits in varying degrees of formation to the side of a metacarpus or phalanx by ankylosis or articulation.

Hexadactyly is commonest, but cases of 7, 8, 10, 12, and even 13 digits upon one or more extremity have been recorded.

In the Laurence-Moon syndrome, all the reported cases show the polydactyly in the post-axial site. In no observed case was there more than one extra digit. Symmetrical polydactyly, i.e. an extra digit on each extremity, is reported by a number of observers, as has already been shown; but non-symmetrical distribution is the more common.

Mere nodules (type (a) see above), are reported by McAlpine on the left hand of a case showing fully developed supernumerary toes; similar appendages on the hands in a case with supernumerary toes is reported by Griffiths.

Bifurcation of the upper end of the metacarpal (type (β)) carrying a complete finger is illustrated by Denzler. A similar condition in the foot, associated with polydactyly in the hand intermediate in type between this form and type (γ) is reported by Bertelotti. Bifurcation at lower end of the metatarsals is shown in a case in our second group. In Bailliart and Schiff-Wertheimer's case the supernumerary fingers consisted of phalanges while the supernumerary toes had well-developed metatarsals of their own.

In von Jaksch's case there was stunting of the fourth and fifth fingers of the left hand together with fusion of the third and fourth metacarpals in both hands. That syndactyly occurs as a replacement or addition to the polydactyly has already been noted.

In the thirty isolated cases reported in the literature, polydactyly was absent in four. In the seven familial groups (forty-one cases) it was absent in twelve cases, in two of which syndactyly was, however, present. In our own cases it was absent in two out of three in our first groups and present in all three cases of our second group.

(c) *Mental developments.* Mental defect may be in the nature of failure of development or of a disintegration of a fully developed mentality. Apart from the fact that in the few cases already mentioned, the mental changes were slight (Rieger and Trauner, Biedl and Raab, Bernhardt, Clay, Ornsteen, Willi), most observers state that the children were backward from early infancy. An apparently normal development of mentality until childhood is reported by Beck, Wuite, and Lisser: McAlpine speaks of his case as not showing ' true dementia '—a view which seems also to be held by Ritter. As already noted, Dr. A. C. Williams reported on our first group as having a ' defect rather more of the type that is usually associated with cerebral lesions than with primary amentia '.

(d) *Adiposity.* Obesity is present in all the reported cases, and was present in all but one of our own cases (the third in our first group). This boy has, however, been growing distinctly fat during the past two years.

It is held that at least 80 per cent. of cases of obesity do not conform to any characteristic type. Though a causative classification is inapplicable in most cases, some cases of obesity do, however, conform to definite recognized types.

(1) *Thyrogenic.* In typical cases the characteristic picture of myxoedema is produced. The fat tends to be laid down round the extremities and peripheral joints, at the fingers and toes, and particularly above and below the clavicles.

(2) *Hypophyseal.* This is typically seen in the Fröhlich syndrome. The

fat is increased in the proximal parts of the limbs; abdomen, above the pubes, around the hips and buttocks, and at the thorax, exaggerating the normal contours in the female and producing a feminine outline in the male. In males after puberty the skin remains smooth, hair is absent or sparse, and of a feminine distribution when present. In contrast to this variety is the Cushing type of pituitary adiposity, in which the fat is deposited over the trunk and face, leaving the arms rather thin by contrast. The skin is coarse, marked by pigmented atrophic striae over the abdomen, buttocks, and thighs, and is very hairy over the face. It is possible that this type is not pituitary but suprarenal in origin.

(3) *Adrenal.* This is seen in the adreno-genital syndrome. Gross adiposity of the Cushing type is associated with virilism in both sexes and a progressive lassitude and cachexia.

(4) *Cerebral and cerebellar* types are probably caused indirectly by disturbances in the hypothalamic and pituitary regions. The existence of fat regulating centres in the forebrain has been demonstrated experimentally by Raab, Wertheimer, and others, and probably accounts for the obesity sometimes following encephalitis lethargica.

That the obesity in the Laurence-Moon-Biedl syndrome is of the Fröhlich type is obvious from the published photographs and descriptions of most of the adult cases. It is, however, to be noted that hypogenitalism is not invariably present. Of interest in this connexion is the case reported by Denzler and subsequently by Willi. Denzler found a boy at the age of 12½ to be 'monstrously fat'; the distribution of the fat was uniform, showing no preference for any particular site. Denzler also found the external genitalia markedly hypoplastic. But at the age of 23, examined by Willi, there was no hypogenitalism; and the adiposity now conformed to the cerebral type.

Milder degrees of hypogenitalism are not easily determined in boys, and totally undeterminable in girls before puberty. On these points case reports are frequently inconclusive.

(e) *Pathology.* There is a considerable discussion in the literature as to the nature of the affection. As most observers report negative radiographic findings on the sella turcica, the suggestion has been advanced that the lesion is hypothalamic rather than pituitary in origin. Since no case has come to post-mortem examination nothing definite can be said at this stage.

(f) *Genetic behaviour.* (1) *Ratio of affected to normal children.* If the 43 sibships, in which the number of both normal and abnormal children is known, are taken, the ratio of affected to normal members is 75 : 107 (1 : 1·42). The ratio in the case of recessive defects in man is always nearer 1 : 2 than 1 : 3 owing to the fact that the children of two heterozygotes cannot be recognized and counted, unless one or more inherits the defect, and with the small families so common in man sibships without an abnormal member are not infrequent. In this case, however, the ratio is

farther from the 1:3 ratio than usual, and this is probably due to the fact that a large number of normal sibs died in infancy or childhood. If the children who died young are taken into account, and those with poly-dactyly are regarded as having the Laurence-Moon syndrome and the rest as normal, the ratio of affected to normal is 85:146 (1:1·71), which is very close to the ratio found in rare recessive defects such as xeroderma pigmen-tosum. In the families with juvenile amaurotic idiocy studied by Sjögren the ratio was 115:189 (1:1·6).

(2) *Sex ratio.* In the 43 complete sibships the ratio of affected males to affected females is 44:28, and in 3 cases the sex is not stated; while of the members of these sibships who died young, and are known to have had polydactyly, 4 were males, 3 females, and 3 of unstated sex. Thus there is no evidence that more affected females than males died at an early age. In the 20 sibships, of which full details are lacking, the ratio of affected males to affected females is 17:12, and in all taken together 61:40. There appears to be a real preponderance of males over females with the defect. Unfortunately the sex of the normal sibs in the complete sibships is not stated in 43 cases, but of those whose sex is mentioned 30 were males and 31 females, and these figures do not suggest that there was any notable inequality in the sex ratio of the normal members.

In juvenile amaurotic idiocy Sjögren found, in sibs with the defect, a ratio of males to females of 61:54, and in their normal brothers and sisters the ratio was 107:82, and only in 9 who died young was the sex unknown. Thus the excess of males with juvenile amaurotic idiocy is no greater than the excess of normal males in the same sibships, and the incidence of the defect may be considered to fall equally on the two sexes.

(3) *Consanguinity of parents.* Taking the complete sibships first, there are 23 in which there is definite information about the presence or absence of consanguinity in the parents. Of these 6 were the offspring of marriages between first cousins, the parents of 3 were second cousins, and in the remaining 14 the parents were unrelated by blood, so that 26 per cent. were the result of marriages between first cousins, and 43 per cent. were the result of marriages between first or second cousins. If the 20 remaining sibships, in which no statement is made about the consanguinity or other-wise of the parents, are added, nearly 14 per cent. were the result of the marriages between first cousins, and about 23 per cent. were the result of marriages between first or second cousins. It is interesting to compare these figures with those found in the infantile form of amaurotic idiocy (Tay-Sachs disease) in which Slome says that the percentage arising from marriages between first cousins lies between 15 and 19·8, that for Jewish cases being between 11·9 and 16, and for Gentile cases between 33·3 and 40. If the incomplete sibships are taken into account the figures are a much less reliable index of the real percentage of first cousin and consanguineous marriages. Of those about which information is available concerning the consanguinity of the parents, 7 were the offspring of first cousins (27 per

cent.), 10 were the offspring of first or second cousins (38 per cent.), in 16 the parents were not blood relations, and in one consanguinity was suspected but not proved. If the 56 sibships, in which there is no mention of the consanguinity of the parents, are counted as born of unrelated parents, the percentage arising from marriages between first cousins is 12·9 and from consanguineous marriages 18.

In nearly every case it is stated definitely that the parents were both normal, and though no ascendant is known to have had the complete syndrome, polydactyly was present in a paternal uncle of Deusch's patient and in a maternal uncle of one of Lisser's patients, and it is probable that they had the other defects as well.

(4) *Mode of inheritance.* There is then no reason to doubt that the syndrome is inherited as an autosomal recessive, but it is most unlikely that a mutation of a single gene causes both the skeletal defects, and the retinal changes with mental deficiency, obesity, and hypogenitalism. The polydactyly and other skeletal defects are due to an abnormal division of the primitive mesenchyme, or to some other mesodermal error of development, whereas the rest of the syndrome depends upon an abnormality of the retina and diencephalon, which are epiblastic.

Rieger and Trauner believe that the meso- and epiblastic parts of the syndrome are recessive and are due to mutations of two genes in the same chromosome, a suggestion made independently by one of us in a book published four years later than their paper. (E. A. C., *Inherited Abnormalities of the Skin and its Appendages*, p. 40, London, 1933.) Bauer, however, says that polydactyly is dominant, and points out that it sometimes skips a generation, and he thinks that in this syndrome it is dominant and independent of the retinal and cerebral changes, which are recessive. Pedigrees of the dominant form of polydactyly very rarely fail to show direct descent, and it would be most improbable that all the parents of individuals with this syndrome would escape the polydactyly if it were dominant, and that there would be only two cases of its appearance in ascendants, and those not in the direct line of descent. We think that there can be little doubt that Rieger and Trauner are right in believing that both parts of the syndrome are recessive and that it is an example of linkage.

The variation in the epiblastic part of the syndrome found in members of different families or even in members of the same sibship is no greater than in many recessive abnormalities due to single gene substitutions. The polydactyly is very variable; sometimes all four extremities have six digits, in others only the hands or the feet are affected, and in a few only one hand or foot is polydactylous. In some the extra post-axial digit is very small and fibrous with no alteration in the bones, in others there is a bifid fifth metacarpal or metatarsal with a sixth finger or toe with the full complement of phalanges, and occasionally there is a complete sixth metatarsal and toe. Even in members of the same sibship these different

grades of polydactyly may be present. In a few patients with the epi-blastic part of the syndrome there is no polydactyly. This was so in two of the four affected members of the sibship reported by Solis-Cohen and Weiss, in one of the three in the sibship reported by Looft, and in two of the three in the first sibship described in this paper. If crossing over were the cause of these examples of the incomplete syndrome, one would expect some members of these sibships to have had polydactyly without the retinal and cerebral changes, but, though all the sibships were large, only two had polydactyly alone. A more probable explanation is that an individual may be genetically polydactylous without showing any visible polydactyly, as has been proved to occur in guinea-pigs with a dominant form of poly-dactyly. If this is so, the sibships recorded by Laurence and Moon, Orn-steen, and Reilly and Lisser can be accepted as examples of the Laurence-Moon-Biedl syndrome, the affected members being genotypically polydac-tylous with cerebral and retinal defects, but phenotypically normal in the development of the extremities. The most convincing evidence in favour of this is the family described by Clay. For in the one sibship the affected children had polydactyly, but in the other sibship, cousins of the first, the affected child had no polydactyly, though the fingers were short and thick and were all of equal length, and the second and third toes of both feet were webbed.

In the family described by Willi there was no polydactyly, but webbing of the proximal phalanges of the fingers and toes and complete syndactyly of the little and ring fingers, and of the third and fourth toes of both feet were present in both the brother and sister, and their hands and feet were small and broad. In the boy recorded by Sterling there was syndactyly, webbing of the three middle toes on each foot, which is uncommon. It is probable that in both these families the webbing and other abnormalities of the extremities are caused by the same recessive gene that causes the poly-dactyly, and it is possible that other skeletal defects may be due to its action, such as the shortness of stature, which is almost always present, the short arms (Bertelotti) and the coxa vara (Willi), dislocation of both patellae and partial doubling of the thumbs (Turner), short fourth and fifth metacarpals of the left hand (von Jaksch).

Webbing of the second and third toes has been noticed by Clay, Griffiths, Turner, Beck, and others, and this may be an independent anomaly, since it occurred in two normal sisters of Griffiths' patient.

The condition is a very rare one, but it has occurred in Latin races (French, Italian, and Spanish), and in Teutonic races (English, American, and Norwegian), and has been recorded from Europe and from both North and South America, but has not yet been described in Negroes, Mongols, or any of the races of India. There is little doubt that some mutations have occurred again and again, and the occurrence of the same defect in various races is no proof of a common origin, since the mutation may have arisen independently in each, but the chances are very remote that two genes in

the same chromosome would mutate together, each in the same way, on two separate occasions, and it is probable that the families, in which the Laurence-Moon-Biedl syndrome has appeared, are all descended from a single individual in whom the double mutation took place, though, if this is the case, the mutation must be a very ancient one.

(g) *Relationship to ' Juvenile Amaurotic Idiocy '*.   The term juvenile amaurotic idiocy applied to a group of cases also known under a variety of other names (Batten-Mayou disease, Vogt-Spielmayer disease, Oatman's disease, cerebro-macular degeneration, familial progressive macular degeneration with dementia, retino-cerebral degeneration), represents an attempt to link up the condition with Tay-Sachs disease, which in contrast is named infantile amaurotic idiocy.   That these two conditions have no real connexion is now accepted by most observers : the difference in racial distribution and genetic behaviour (Slome, Sjögren) is enough evidence to this effect quite apart from the different pathological basis.   But if there is no relationship between these two forms of severe nervous disease, it is of interest to inquire into a possible relationship between ' juvenile amaurotic idiocy ' and the Laurence-Moon-Biedl syndrome.

In the classical cases of juvenile amaurotic idiocy reported in this country —those of Batten and Mayou—and most of the subsequent cases, emphasis was laid on the presence of a macular lesion in the form of ' stippling '. On the continent, Vogt described optic atrophy and Spielmayer appearances of retinitis pigmentosa as the characteristic fundus lesions. It would appear that actually these appearances are different stages of a progressive process, as is suggested by Holmes and Paton by their classification of three stages, well shown in one single family under their observation : ' 1st stage : retina generally normal in appearance except a small white area at macula surrounded by a red ring ; 2nd stage : the white area with red ring accentuated at the macula, wavy white streaks in the perimacular area and pale disk with arteries reduced in calibre ; 3rd stage : extensive macular change, peripheral retinal atrophy and optic atrophy, and thread-like arteries '. In the third stage the appearances in their case was ' to a slight degree the spider-web appearance of retinitis pigmentosa '. Sjögren, in his review on the subject, concludes that the fundus appearances present a fairly changeable picture. In the majority of cases, appearances similar to retinitis pigmentosa are seen ; in others, chorioretinitis and optic atrophy are present. Macular lesions, as characteristic features, do not seem to be stressed by continental observers.

This inconstancy in ophthalmoscopic findings in juvenile amaurotic idiocy has an interesting parallel in the Laurence-Moon-Biedl syndrome.

Here too, the picture is most variable—from stippling of the macula and optic atrophy to typical retinitis pigmentosa with atypical retinitis pigmentosa as a variant in the majority of cases. The possible relationship between these conditions has indeed already been raised by Velhagen, who rightly points out that ophthalmoscopically they are indistinguishable.

There are, however, certain features which make it difficult to link the two conditions together. (1) *The mode of onset*. Practically all reports on cases of juvenile amaurotic idiocy lay stress on the fact that the children were normal until the onset of the affection at the second dentition ; an earlier history of mental backwardness in juvenile amaurotic idiocy is the exception, just as it is the exception to find a normal mentality and normal early development in cases of the Laurence-Moon-Biedl syndrome. (2) *The course*. The increasing failure of vision, increasing dementia, paralysis, end in the onset of epileptic fits, and the death, usually at 14–16 years of age, is in marked contrast to the slow, almost non-progressive, course of the Laurence-Moon-Biedl syndrome. Though the syndrome has now been well-recognized for more than twelve years no post-mortem record is as yet available. (3) *Neurologically* juvenile amaurotic idiocy gives a characteristic picture of a progressive upper motor-neurone lesion. The Laurence-Moon-Biedl syndrome is neurologically silent. In this connexion it should, however, be pointed out that the cases of Laurence, seen nine years later by Hutchinson, struck that great observer as cases of paraplegia. The ' slouching gait ' recorded earlier by Laurence is significant in this connexion [? coxa vara]. (4) *The associated conditions*. Hypogenitalism and adiposity are mentioned by Erdmann and by Schall in their cases of juvenile amaurotic idiocy. In view of the fact that this is not observed by Sjögren in his study of no less than fifty families, and that he noted syndactyly but once and polydactyly not at all, the observations by Erdmann and Schall are interesting rather than conclusive. Erdmann's cases may very likely have been cases of the Laurence-Moon-Biedl syndrome. (5) *The Genetic behaviour*. It would appear that whilst both the Laurence-Moon-Biedl syndrome and cerebromacular degeneration are recessive, there is a difference in the sex incidence. There is a considerable excess of males with the syndrome and no real excess of males in juvenile amaurotic idiocy.

Summary

Two families are reported, one of ten members of whom three, and possibly four, were affected, and another of four members of whom three were affected.   There was no consanguinity of parents in either group.

In the first group no member showed the complete syndrome, but all the constituents of the syndrome were seen between the three patients.   The eldest, aged 26, showed moderate adiposity, mental retardation, and retinitis pigmentosa ; there was no polydactyly and no obvious hypogenitalism. The second showed the complete Fröhlich syndrome, mental retardation, and retinitis pigmentosa ; there was no polydactyly.   The third showed polydactyly in both hands in addition to mental retardation and retinitis pigmentosa ; he showed neither adiposity nor hypogenitalism.

In the second family polydactyly was present in all three : on the left hand and both feet in the eldest, on all the four extremities in the second,

Genetic Analysis

(a) Complete Sibship

Author's name	No.	♂	♀	●	♂	♀	●	♂	♀	O	Consanguinity of parents	Remarks	Nationality
Bardet (Chaillous)	1												French
Beck	4	1	1			2					—	—	Italian
Bell, more fully reported in this paper	4	1				2					None	—	English
Bernhardt	4	2									None	♂died soon after birth. No polydactyly Oeviscerated owing to mother's narrow pelvis	Polish Jew
Bertelotti	4	1*	1		1					3	None	—	—
Biedl, Raab	6	1*	1		1						None	*Atresia ani ♂died at 2 years, polydactyly, 6 toes on each foot †died at 3 weeks, polydactyly, said to have had 7 toes on each foot ♂died at 9 months, normal	—
Bing	6	1	1							4	—	♀died in infancy	? Norwegian
Boenheim	2	1	1								None		Father = German, Mother = Italian
Borchardt	4	2			1						2nd cousins		—
Clay	3	2			1					3	2nd cousins	The affected sibships were cousins	—
Denzler (Willi)	5	1				2					None	Odied at 2 months, spina bifida	—
Deusch	6	1	1							3	—	Odied a few days old, diarrhoea ●died at 3 months, congenital morbus cordis, 6 fingers on each hand	—
Feeder	5	2			1			2			—	●died in infancy, 6 fingers on one hand	—
Griffiths	6		1*		1			2*			—	*Webbed toes ♀died at 10 days, 6 digits on all four extremities	—
Grossman	3	2*			1			1			None	*stillborn, deformed head *one had congenital morbus cordis	Austrian
von Jaksch	4	1				1				3	—	5 died young, 4 of convulsions	German
Lange	8	1	1		1			1			1st cousins	●died at 2¼ years, polydactyly, could walk, but not talk	German
Lange	13	1								10	—	2 died young 1 miscarriage just before birth of affected boy	German
Lange	9	1								3	—	5 died young 1 miscarriage	German
Laurence, Moon	10	3	1			6					None	—	English

Name						Consanguinity	Notes	Nationality
Lisser	7	—	1	3	—	—	●died at 6 months, 6 toes on each foot	Spanish
Looft	9	1	—	—	6	—	Odied at 13 months / Odied at 14 months / Odied, pneumonia	—
Looft	7	1	1	—	2	—	OOdied in infancy / ●died in infancy, 6 toes on each foot	—
McAlpine	7	1	—	2	—	None	—	Polish
McCrae, Weiss (Weiss b)	2	—	1	4	—	—	—	—
Madigan, Moore	2	1	—	—	—	—	♂died at 2 weeks / 1 miscarriage	American
Orgaz	7	3	—	1	3	Cousins 2nd grade	Opremature / 3 miscarriages	—
Ornsteen	6	1	2	2	1	None	Odied young, epilepsy	American
Poos (Pagels)	9	—	3	—	3	1st cousins	Odied, gastro-enteritis / Odied, nystagmus, idiocy	—
Reilly, Lisser	5	—	2	2	1	None	Odied at 6 days, imperforate anus, no polydactyly	—
Ricaldoni, Isola	8	2	2	—	—	1st cousins	Odied at 11 years, meningitis / Odied at 2 days / Ostillborn	—
Rieger, Trauner	6	—	1	—	3	1st cousins	●died at 6 months, polydactyly	—
Ritter (Velhagen)	2	1	—	1	1	1st cousins	—	Russian Jew
Rowe	3	1	1	—	—	—	—	—
Serejski	5	1	1	—	—	—	OOdied in infancy	Italian
Solis-Cohen, Weiss (Hansell)	8	2	2	1	—	None	1 miscarriage	—
Turner	4	1	—	1	—	—	♂} twins {died at 1 month / stillborn} ♂} / 3 miscarriages	—
Weill, Payeur	2	1	—	1	1	1st cousins	*does not see well, not examined	—
Willi	3	1	1*	—	2	None	—	—
Wuite	3	1	—	3	—	—	—	—
Zondek	4	1	—	3	—	—	—	—
New record	10	2	1	4	2	None	●died in infancy, 6 fingers on each hand	English
	44	28	3	30	31	46		
		75			107			

(b) Incomplete Sibships

Author's name.	♂	♀	Consanguinity of parents.	Nationality.
Bailliart, Schiff-Wertheimer	—	1	—	—
Bailliart, Schiff-Wertheimer	—	1	—	—
Bauer	1	—	—	—
Bauer	1	1	1st cousins	—
Biedl, Raab	1	—	—	—
Boenheim	—	1	—	Jewish
Braunstein	—	1	—	—
Braunstein	1	—	—	—
de Cyon	3	—	—	—
Farnés	2	—	—	—
Friedmann	1	1	—	—
Gordon	1	1	—	Jewish
Herzog	2	—	—	Jewish
McKinney	—	1	—	—
Poos	1	1	—	—
De Schweinitz	—	1	Doubtful	—
De Schweinitz	—	1	None	—
De Schweinitz	1	—	None	—
Sievert (Krükmann, Meyer)	1	1	—	—
Sterling	1	—	—	—
	17	12		

and on the two hands but not on the feet in the third. Adiposity and mental retardation were present in all the three, as also moderate hypogenitalism in the eldest. The fundi showed the appearances seen in cerebromacular disease.

We wish to express our indebtedness to Dr. T. R. Hill and Mr. J. H. Gurley for permission to study the B. family now under their care, and to Dr. A. C. Williams for his report on the mental condition of the A. family.

REFERENCES

Bailliart and Schiff-Wertheimer, *Bull. Soc. d'Ophthal. de Paris*, (a) 1931, 350 ; (b) 1932, 74.

Bardet, G., *Univ. Paris Thesis*, 470, 107, 1920.

Bauer, J., *Innere Sekretion*, 1927, Berl. u. Wien.

Beck, H., *Endocrinology*, Los Angeles, 1929, xiii. 375.

Bell, Julia, (a) *Ann. of Eugen.*, Camb., 1930–1, iv. 41 ; (b) *Nettleship Memorial*, ii. 1, 1922.

Bernhardt, H., *Ztschr. f. klin. Med.*, Berl., 1928, cvii. 488.

Bertelotti, M., *Nouvelle iconographie de la Salpétière*, Paris, 1914–15, xxvii. 11.

Biedl, A., and Raab, W., *Deutsch. med. Wchnschr.*, Leipz., 1922, xlviii. 1630 ; *Wien. Arch. f. inn. Med.*, 1924, vii. 443.

Bing, R., *Norsk Mag. f. Laegevidensk.*, Kristiania, 1931, xcii. 933 ; Abstr. *Journ. Amer. Med. Assoc.*, Chicago, 1932, xcviii. 440.

Boenheim, F., (a) *Endokrinologie*, Leipz., 1929, iv. 263 ; (b) *Ztschr. f. Augenheilk.*, Berl., 1932, lxxvi. 156.

Borchardt, L., *Endokrinologie*, Leipz., 1932, x. 250.

Braunstein, E., *Arch. f. Ophthal.*, Berl., 1924, cxv. 438.

Chaillous, *Ann. d'Ocul.*, Paris, 1921, clviii. 100.

Clay, G. E., *Trans. Amer. Ophthal. Soc.*, N. York, 1933, xxxi. 274.

de Cyon, *Bull. Acad. de Méd.*, Paris, 1928, xl. 444.

Darrier, A., *Arch. d'Ophthal.*, Paris, 1887, vii. 170.

Denzler, E., *Jahrb. f. Kinderh.*, Berl., 1925, cvii. 35.

Deusch, G., *Deutsche Ztschr. f. Nervenheilk.*, Berl., 1925, lxxxvii. 117.

Erdmann, L., *Ztschr. f. Augenheilk.*, Berl., 1924–5, liv. 84.

Feeder, *ibid.*, 1930, lxxii. 244.

Friedmann, M., *Zentralbl. f. Haut- und Geschlechtskr.*, Berl., 1932, xli. 544.

Gordon, A., *N. York Med. Journ.*, 1907, lxxxv. 294.

Griffiths, E., *Journ. Neurol. and Psychopath.*, Lond., 1931, xii. 53.

Grossman, E., *Wien. med. Wchnschr.*, 1908, lviii. 742.

Hansell, H. F., *Amer. Journ. Ophthal.*, Chicago, 1925, viii. 374.

Herrlinger, C. L., *Ueber die Aetiologie der Retinitis pigmentosa*, Thesis Tübingen, 1889.

Herzog, *Klin. Monatsbl. f. Augenh.*, Stuttgart, 1929, lxxxii. 117.

Hill, T. R., and Sorsby, A., *Proc. Roy. Soc. Med.*, Lond., 1934, xxvii. 1613.

Höring, Jnr., *Klin. Monatsbl. f. Augenheilk.*, Erlangen, 1864, ii. 233.

Hutchinson, J., (a) *Ophthal. Rev.*, Lond., 1882, i. 28 ; (b) *Arch. Surg.*, by J. Hutchinson, London, 1900, xi. 118.

von Jaksch, R., *Med. Klin.*, Berl., 1912, viii. 1931.

Krückman and Meyer, *Deutsche med. Wchnschr.*, Leipz., 1908, xxxiv. 574.

Lange, W., *Allg. Ztschr. f. Psychiat.*, Berl., 1927, lxxxvi. 404.

Laurence, J. Z., and Moon, R. C., *Ophth. Rev.*, Lond., 1866, ii. 32.

Leber, Th., *Die Krankheiten der Netzhaut*, p. 1187 in Graefe-Saemisch, 2te. Aufl., Bd. 7, Theil ii, Kap. x, Aii, Leipz. u. Berl. 1916.

Lisser, H., *Endocrinology*, Los Angeles, 1929, xiii. 533.

Looft, C., *Acta Paedriatica*, Stockholm, 1932, xiii. 322.

McAlpine, D., *Proc. Roy. Soc. Med.*, Lond., 1924–5, xviii. Sect. Neurol., 30.

McCrae, I., and Weiss, E., *Med. Clin. N. Amer.*, Philad., 1931, xiv. 825.

McKinney, J. M., *Journ. Nerv. and Ment. Dis.*, N. York, 1931, lxxiv. 50.

Madigan, J. J., and Moore, J. V., *Journ. Amer. Med. Assoc.*, Chicago, 1918, lxx. 669.

Nettleship, E., *Ophthal. Hosp. Repts.*, 1908 ; xviii. 371.

Ornsteen, A., *Amer. Journ. Med. Sci.*, Philad., 1932, clxxxiii. 256.

Orgaz, J., *Rev. méd. latino-am.*, Buenos Aires, 1931, xvi. 966.

Poos, *Klin. Monatsbl. f. Augenh.*, Stuttgart, 1929, lxxxii. 532.

Raab, O., *Ztschr. f. d. ges. exper. Med.*, Berl., 1926, xlix. 179.

Ratner, J., *Monatschr. f. Psychiat. u. Neurol.*, Berl., 1927, lxiv. 283.

Reilly, W. A., and Lisser, H., *Endocrinology*, Los Angeles, 1932, xvi. 337.

Ricaldoni, M., and Isola, A., *Bull. et mém. Soc. méd. des hôp. de Paris*, 1928, lii. 1131.

Rieger and Trauner, *Ztschr. f. Augenheilk.*, Berl., 1929, lxviii. 235.

Ritter, F. H., *Ztschr. f. ges. Neurol. u. Psychiat.*, Berl., 1932, cxli. 402.

Rowe, S. N., *Arch. of Neurol. and Psychiatry*, Chicago, 1931, xxv. 898.

Rozabel-Farnès, *Rev. clin. de Madrid*, 1913, lx. 401.

Schall, E., *Arch. f. Ophthal.*, Berl., 1926, cxvii. 702.

de Schweinitz, G., *Tr. Ophth. Soc. U. Kingdom*, Lond., 1923, xliii. 90.

Serejski, M. J., *Med. klin.*, Berl, 1929, xxv. 1620.

Siegheim, M., *Beiträge zur Kenntnis der Retinitis pigmentosa*, Thesis Breslau, 1886.

Sievert, H., *Ztschr. f. Augenheilk*, Berl., 1908, xix. 544.

Sjögren, T. S., *Hereditas*, Sweden, 1931, xiv. 197.

Slome, D., *Journ. of Genetics*, Lond., 1933, xxix. 363.

Solis-Cohen, S., and Weiss, E., *Amer. Journ. Med. Sci.*, Philad., 1925, clxix. 489.

Sterling, W., *Polska Gaz. lekar*, Lwów, 1930, xlv. 889 ; also in *Rev. neurol.*, Paris, 1930, xxxvii. i. 661.

Stör, *Klin. Monatsbl. f. Augenh.*, Erlangen, 1865, iii. 23.

Turner, H., *Journ. Oklahoma M. A.*, 1931, xxiv. 148.

Velhagen, K., *Klin. Monatsbl. f. Augenh.*, Stuttgart, 1932, lxxxix. 1.

De Wecker, L., *Traité théorique et pratique des maladies des yeux*, Paris, 1866, tome ii. 351.

Weill, G., and Payeur, P., *Bull. Soc. d'Ophthal. de Paris*, 1933, 293.

Weiss, E., (a) *Amer. Journ. Med. Sci.*, Philad., 1932, clxxxiii. 268 ; (b) *Endocrinology*, Los Angeles, 1931, xv. 435.

Wertheimer, F., *Pflüger's Arch.*, Berl., 1926, ccxiii. 262.

Wibaut, F., *Klin. Monatsbl. f. Augenh.*, Stuttgart, 1931, lxxxvii. 298.

Wider, A., *Ueber die Aetiologie der Retinitis pigmentosa*, Thesis Tübingen 1885.
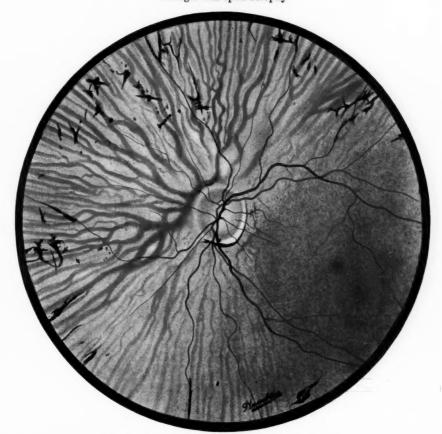
Willi, H., *Jahrb. f. Kinderh.*, Berl., 1931, xiii. 133.

Wuite, J. J., *Nederl. tijdschr. v. geneesk.*, Amsterdam, 1932, lxxvi. 1102.
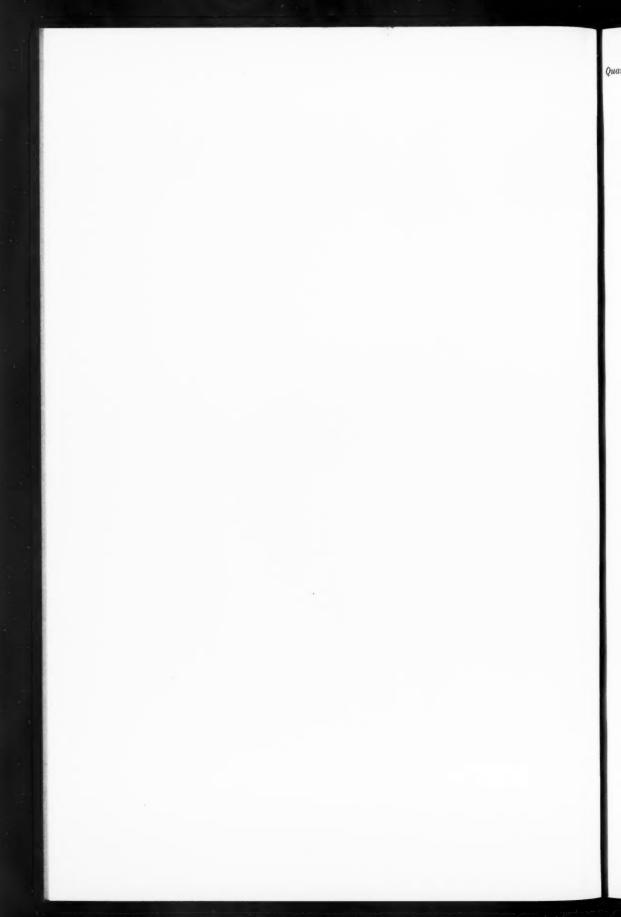
Zondek, H., *Die Krankheiten der Endokrinen Drusen*, Berl., 1926.
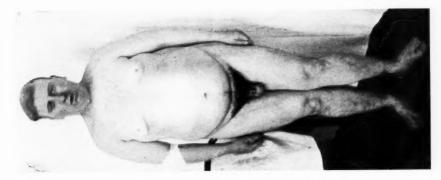
Right fundus oculi of Cynthia B. Showing macular
changes and optic atrophy
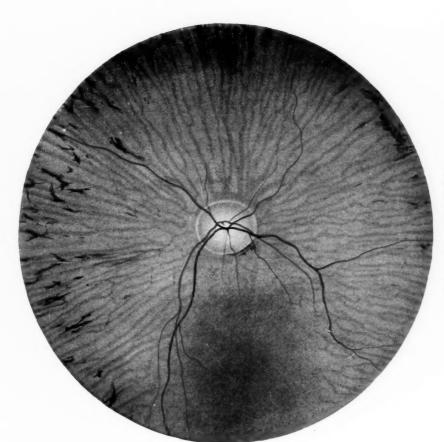
Left fundus of Martha A. Showing typical retinitis
pigmentosa
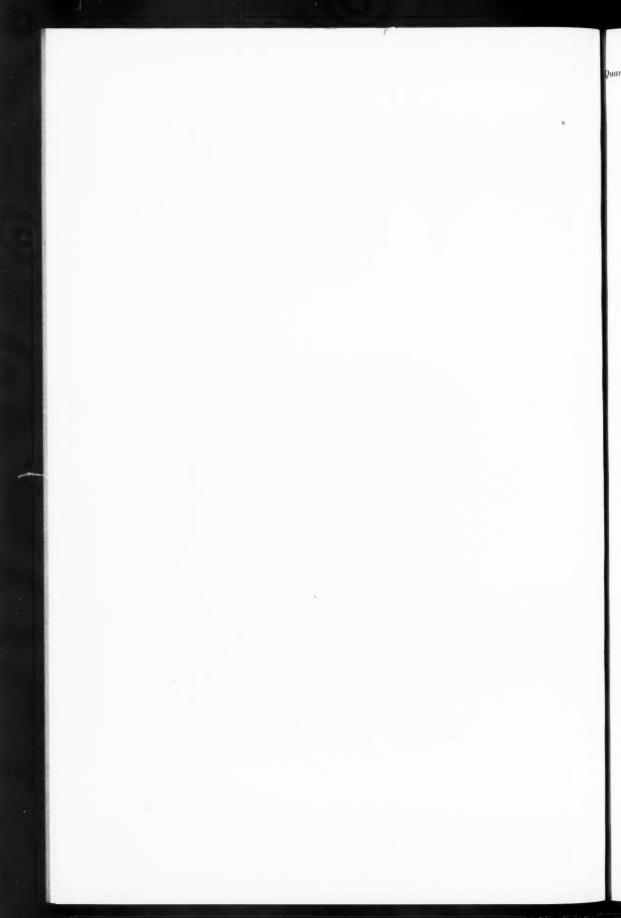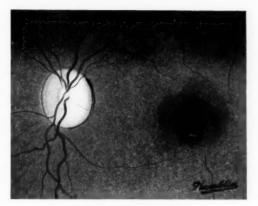
Photograph of Edward A., the second member of the first group
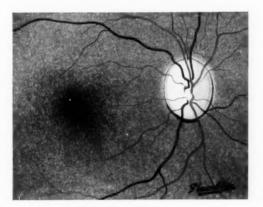
Right fundus of Edward A.
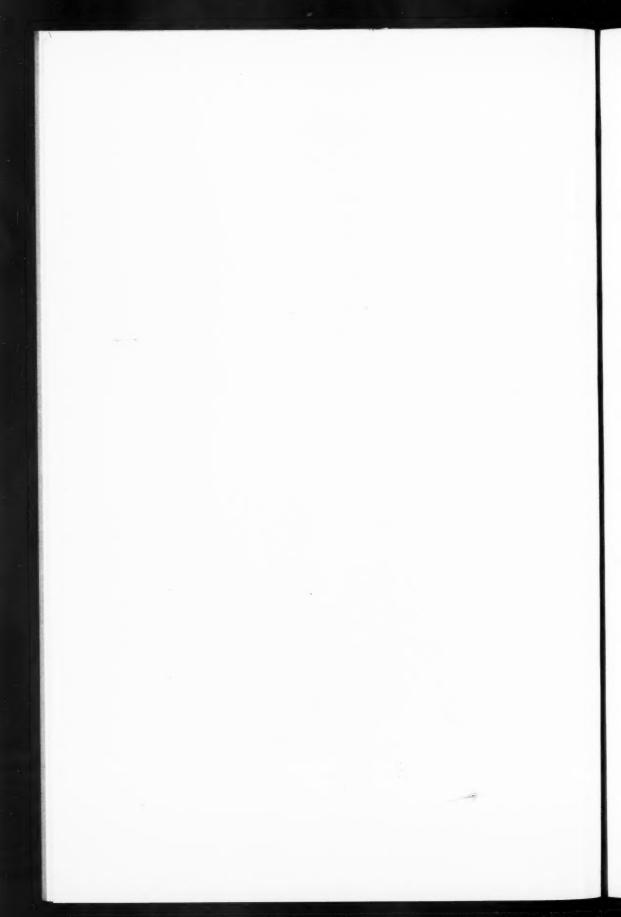
Left fundus of Patricia B.

Right fundus of Patricia B.

Left fundus of Cynthia B.

616–003.829.1

HAEMOCHROMATOSIS [1]

1, THE CONTENT OF THE TISSUES IN IRON AND SULPHUR
2. THE RESULTS OF SPECTROGRAPHIC EXAMINATION WITH ESPECIAL REFERENCE TO COPPER AND CALCIUM

By HUGH RAMAGE AND JOSEPH HAROLD SHELDON

With Plate 12

HAEMOCHROMATOSIS is a disease offering but rare opportunities for investigation. It has, however, been possible to examine the tissues from five patients, the results of which are described below. (Two of the cases (B. and R.) were under personal observation at Wolverhampton, while we are indebted to Dr. R. A. McCance of King's College Hospital, London, Dr. C. J. Polson of St. James's Hospital, Leeds, and Dr. W. S. Stewart of the Royal Infirmary, Worcester, for tissues from the remaining three. The diagnosis was established in all cases by the autopsy.)

1. *Iron*

It has been known for a long time that extensive deposits of iron occur in this disease, but attention has mainly been confined to the larger organs, such as the liver, spleen, kidneys, and pancreas. In a previous investigation (Sheldon, 1927) a larger number of tissues was examined and a raised content of iron was found in all, including the brain, and it was estimated that the body contained an approximate total of 40 grm. of iron. The iron was estimated by the method of Neumann, and it was thought advisable to repeat this work on the present cases with a more accurate method, since that of Neumann had been subjected to criticism. Kennedy's method (1927) was used, the tissues being ashed by heat after previous drying at 100° C. The results are set out in Table I for four of the cases examined.

1. The figures indicating the degree of excess of iron content over the normal are not more than approximate, owing to the difficulty of obtaining reliable control figures. In certain organs (e.g. liver) there may be wide individual differences, and in others it is impossible to free post-mortem specimens from blood. This applies especially to the lungs, spleen, and choroid plexuses, in which the figures for normal are probably too high, with the result that the excess in the diseased tissues does not appear as great as it is histologically. This applies with special force to the choroid plexuses, owing to their

combined vascularity and small size. It is, however, significant that the iron values of the tissues from haemochromatosis exceed the normal in almost all instances, and in some tissues the difference is enormous. Organs such as the liver, pancreas, and salivary glands may have from fifty to a hundred-fold increase.

TABLE I

Fe in mg. per 100 grm. (dry tissue)

Tissue.	Control tissue.	Case B.	Case R.	Case S.	Case McC.	Factor of average excess over normal.
1. Liver	50	3613	2120	2440	2155	× 47
2. Pancreas	17·8	1410	2140	2300	871	× 93
3. Spleen	140	265	130	—	370	× 2
4. Kidney	39	102	77	123	116	× 2·5
5. Salivary gland	14	—	780	832	—	× 57
6. Thyroid	22	1170	227	700	204	× 26
7. Lung	220	336	880	—	—	× 3
8. Choroid plexus	139	640	421	647	—	× 4
9. Pituitary	—	—	845	—	—	—
10. Suprarenal	72	435	252	—	—	× 5
11. Testis	13	50	72	—	—	× 5
12. Epididymis	13	—	21	—	—	× 1·5
13. Heart	39	1070	283	550	212	× 13
14. Somatic muscle [2]	25 (4)	105(3)	94 (3)	128 (1)	45 (1)	× 4
15. Stomach	45	280	132	262	—	× 5
16. Duodenum	57	147	115	—	—	× 2
17. Small intestine [3]	28	65	61*	—	—	× 2
18. Large intestine	58	52	63	—	32	—
19. Bone	4·9	18	13·8	—	—	× 3
20. Brain	23	23	24	—	—	—
21. Lymph glands [4]	—	(1) 8440 (2) 3440	3230	—	1360	?
22. Trachea	33	106	—	—	—	× 3
23. Prostate	25	110	—	—	—	× 4
24. Seminal vesicles	—	61	—	—	—	—
25. Gall-bladder	38	72	135	—	—	× 2·5
26. Aorta	19	43	—	—	—	× 2
27. Urinary bladder	18	52	28	—	—	× 2
28. Omentum	33	175	—	—	—	× 5·5

[2] Numbers in brackets refer to the number of muscles analysed in each case—the average result of which is given in the Table.

[3] The jejunum of this case contained the large amount of 0·230 per cent. Fe, while the ileum was much lower (0·61 per cent.).

[4] (1) = Portal gland.
  (2) = Mesenteric gland.

2. The lymphatic glands have the highest figures, particularly the portal and peripancreatic, where the figures reach to 8·44 per cent. There is considerable variation between different glands, depending on their locality and the severity of the case. The highest recorded figure in the literature is that of Anschütz (1899) (14·69 per cent.). These figures have no particular significance in the discussion of the disease, since they only represent iron that has been carried from other parts of the body.

3. Of the true organs, the liver has the highest figures. The iron content of the liver (dry) has now been estimated nineteen times, and varies between

1·04 per cent. (Parmentier and Carrion (1897)), and 7·62 per cent. (Anschütz (1899)), with an average of 3·62 per cent. The cases in the present group show rather low figures. The liver is usually greatly enlarged in haemochromatosis, and the total amount of iron in the organ is therefore very high. The average works out at 24·7 grm., a figure at least four times that found in the whole normal body. The largest individual amount was 38·7 grm. (Aschoff and Hess (1904)).

4. The pancreas comes next to the liver, and in some cases (e.g. R.) the percentage figure may actually exceed that of the liver, though this is rare. There have been nine other estimations on the pancreas, the average figure being 1·89 per cent. The pancreas appears to show a greater degree of individual variation than the liver, the figures varying between 0·584 per cent. (Sheldon (1927)) and 5 per cent. (Anschütz (1899)). The normal pancreas contains less iron than the liver, and the factor of increase over normal is therefore much greater. The pancreas heads the list in this respect, with an increase of nearly a hundredfold.

5. The salivary glands and the pituitary come next. with amounts of the order of 0·8 per cent. No previous estimations have been made on these organs, but the results are in keeping with the histological appearances. There is an increase of some fifty times the normal.

6. The spleen, choroid plexuses, and lungs give average figures in these cases of 0·255, 0·561, and 0·608 per cent. The average for the spleen from the literature (11 analyses) works out at 0·754 per cent., so that these cases are much below the average. The average figure for the lungs (3 analyses) is 0·430 per cent., so that the figures are somewhat higher here. The only other analysis of the choroid plexuses is that of my previous case, where the figure was 0·538 per cent. The increase over normal in these four tissues is probably greatest in the choroid plexuses, and the histological appearances suggest that it greatly exceeds the factor of four shown in the table.

7. The heart and thyroid gland are alike in having figures of the same order of size (0·528 and 0·575 per cent.), though the increase over normal appears to be much greater in the thyroid. In individual cases very high figures may be found in both these organs (e.g. Cases B. and S.).

8. The striated muscle of the body resembles the heart in having an increase of iron. This was found in all the eight specimens that were analysed (pectoralis, quadriceps, psoas, and sartorius), and amounts to an increase of some four times the normal. This is shown in the plate. Owing to their extent, the muscles provide a store of iron in this disease which ranks next to the liver, and exceeds the total amount in the normal body.

9. To a less extent the same appears to apply to bone. The amount is very small, but is about three times normal. (Every precaution was taken to prevent contamination with marrow.)

10. In the alimentary canal, the stomach has the greatest amount (average 0·224 per cent.), or about five times normal, and thence the amount decreases distally, until in the colon the figure of 0·060 per cent. is hardly in excess of

normal. These figures are evidently susceptible of much individual varia-
tion, since in Case R. the jejunum contained as much as 0·230 per cent.,
while the ileum had only 0·061 per cent.

11. In the remaining tissues the figures are not so great, but they almost
invariably show an increase over the normal control figures by a factor
varying from 1·5 to 5. It would appear from these results that the brain
and colon have normal amounts of iron, but this is not of universal applica-
tion. In my previous case the brain contained 2·5 times as much iron as the
control brains.

12. It was not possible to examine the blood of these cases, but the results
obtained by the older methods (Fowler) show that there is no increase in the
total iron of the blood.

There is, therefore, in haemochromatosis a great increase of iron in the
body, which is distributed over nearly all the tissues, and it is pertinent to
inquire into the total amount that may be so stored. The total amount in
the liver has been recorded on fifteen occasions, and varies between 6·85 grm.
(Paviot et al. (1897)) and 38·7 grm. (Aschoff and Hess (1904)), with an
average of 24·7 grm. The amount in the remaining organs is difficult to
assess, but in my previous case, with 16·469 grm. in the liver, the amount
in the lungs, heart, spleen, brain, and kidneys amounted to 2·457 grm., or
roughly a sixth of that in the liver. The content of the thyroid, pancreas,
salivary glands, and lymph glands would certainly exceed this amount, so
that an estimate for the organs of one-fourth that of the liver errs on the
small side. The amount in the muscles has then to be taken into account.
In my previous case this was estimated at 13 grm., and in Cases B. and R.
at about 6·5 grm. These results give figures of 40 grm. of iron in my pre-
vious case, and of about 25 grm. for the other two. Since much greater
amounts have been recorded in the liver than has been found in my three
cases, it is certain that amounts of at least 50 grm. may be found in ad-
vanced cases. These amounts are enormous, and since the iron must have
come from the food, they indicate that the disease must be in progress for
a very long time.

Sulphur. Howard and Stevens (1917) described a retention of sulphur in
metabolic experiments on a case of haemochromatosis, amounting to 0·13 grm.
per day. In recent years French workers have described marked alterations
in the sulphur metabolism in this disease (Loeper, Decourt, and Ollivier
(1926); Even (1932)), stating that there is an increase in the blood sulphur
affecting especially the neutral portion, with a lowering of the ratio oxidized
sulphur / total sulphur. In addition, Loeper found enormous amounts of
sulphur in the tissues (liver 17 per cent.; suprarenals 6·74 per cent.; skin
3·09 per cent.), though the method of analysis is not stated. In view of
these statements, the sulphur content of the tissues from Case B. was in-
vestigated. The dry tissues were analysed by Wolf and Oesterberg's modi-
fication of Benedict's method. The results are shown in Table II. (The
tissues from Dr. Polson's case had been preserved for some time in

glycerine, which may account for their lower values. They give, however, good general confirmation of the grouping of the tissues.)

TABLE II

Sulphur per cent. (dry tissue)

Group.	Tissue.	Haemochromatosis.		Normal tissue.	Ratio of percentage of Case B. to normal percentage.
		Case B.	Dr. Polson's case.		
1. Subnormal	Liver	0·926	1·07	1·49	0·621
	Kidney	0·897	0·593	1·18	0·760
	Spleen	1·00	0·987	1·12	0·893
	Brain	0·683	—·	0·733	0·931
2. Normal	Muscle (quadriceps)	1·03	—	1·09	0·945
	Muscle (psoas)	1·06	—	1·04	1·01
	Thyroid	0·923	—	0·919	1·00
	Heart	1·08	0·895	0·01	1·07
3. Increase over normal	Colon	0·675	—	0·570	1·18
	Ileum	1·01	—	0·731	1·38
	Jejunum	1·09	—	0·774	1·41
	Duodenum	0·865	—	0·611	1·41
	Pancreas	0·865	0·792	0·582	1·48
	Suprarenal	0·844	—	0·561	1·5
	Stomach	1·00	—	0·610	1·64
	Omentum	0·456	—	0·223	2·04

It will be seen that (1) there is no general increase in the sulphur content, and that the figures in no way approach those given by Loeper, Ravier, and Lesure. (2) Certain tissues show a moderate increase in sulphur. They are the suprarenal glands, the pancreas, and the whole length of the alimentary canal. The great omentum shows the most marked increase. The values for the bowel show a steady decrease distally to the colon, where the figure is practically normal. (3) Some tissues (muscle, heart, and thyroid) have normal values, while others (liver, spleen, kidney, and brain) appear to have less than normal. These findings bear no relation to the amount of haemosiderin in the tissues, and indicate that any disturbance of sulphur metabolism is not related to that of iron. Histologically, the tissues having an excess of sulphur tend to show marked deposits of haemofuscin. Inasmuch as this pigment contains sulphur (3·7 per cent. Rosenfeld (1901)), it would appear that any increase of sulphur is related to this pigment.

2. *Spectrographic Examination*

This was carried out by the method of Ramage (1929), the intensities of the lines of the various metals being compared with those of varying strengths of a standard solution. In addition, alternate spectra were produced on numerous plates from both haemochromatotic and normal tissues, to aid in comparison. The results were as follows :—

1. No unexpected elements were found, the differences from normal being quantitative only.

2. Of the elements present in traces in normal tissues, traces of rubidium were found in several specimens. All the livers from haemochromatosis were low in manganese. The control liver contained 0·0006 per cent., and the average found in seventeen livers (Sheldon and Ramage (1931)) was also 0·0006 per cent., while of the haemochromatotic livers four contained only 0·00016 per cent. and the fifth only about half that amount. Since these patients came from widely separated parts of England, this constant low value is probably significant of the disease, and cannot be attributed to the Mn content of the drinking water. Zinc is difficult to detect by the method used, but it has been shown by Herkel (1930) that there is no general retention of this metal in haemochromatosis.

TABLE III

Copper Content of Liver (dry)

Case B.	Case R.	Case S.	Case McC.	Dr. Polson's case.
%	%	%	%	%
0·004	0·04	0·007	0·005	0·009

3. A general increase of copper was found in all the tissues. The results for the liver are shown in Table III. The amounts are high in all the cases, especially in Case R. In Case McC. the spectrographic value of 0·005 per cent. was checked by chemical analysis (for which I am indebted to Dr. R. A. McCance) giving 5·1 mg. per 100 grm. The normal figure for the copper content of the adult liver is about 25 mg. per kilo (dry), so that in haemochromatosis the amount is increased by a factor of between 2–3. This agrees with the results of other workers (cf. Schonheimer and Oshima (1929) ; Herkel (1930)). The same results have also been found in portal cirrhosis, but not in other diseases of the liver.

The only investigation of tissues other than the liver is that of Herkel (1930), who analysed material from three cases. His results, together with the spectrographic results from Case B in this series are shown in Table IV.

TABLE IV

Copper (mg. per kilo (dry tissue))

Tissue.	Normal. (Herkel)	Herkel. (Average of his 3 cases chemical analysis.)	Case B. (Spectrograph.)
Pancreas	8·1	19·8	20
Kidney	25·4	21·7	20
Spleen	9·1	13·6	20
Thyroid	6·3	17·5	25

The chemical and spectrographic figures are in good general agreement. The copper content is raised in the pancreas, spleen, and thyroid, while in all cases the kidney has been less than normal. For the remaining tissues we are dependent on spectrographic analysis only, the results of which are shown in Table V. The omentum, suprarenals, and intestine below the jejunum gave lines which were within normal limits, but the remaining

organs all showed a distinct excess of copper. The lines were strongest in the choroid plexuses. Very careful comparisons were made in the case of striated muscle (quadriceps, psoas, and sartorius), using alternate spectra of normal and diseased tissues on the same plate, and in each case the tissues from haemochromatosis contained roughly twice the normal amount of copper. With the exception, therefore, of the kidney, small bowel, omentum, and suprarenals, all the organs which have been examined in haemochromatosis have more copper than normal. The factor of increase is between two and three times the normal, although in individual cases it may be very much more. Thus the liver in Case R. has at least twenty times the normal.

TABLE V

Copper (spectrographic analysis) as mg. per kilo (dry)

Group.	Tissue.	Haemochromatosis (Case B.)	Normal.
1. Muscle	Quadriceps	16	9
	Psoas	17	10
	Sartorius	23	10
2. Increase over normal	Gall-bladder	25	less than 20
	Bladder	25	,,
	Choroid plexus	45	,,
	Heart	21	,,
	Trachea	31	,,
	Lung	25	,,
	Stomach	27	,,
	Duodenum	40	,,
	Brain	30	,,
	Testis	22	Traces only
	Aorta	19	,,
3. Normal or sub-normal	Suprarenals	16	less than 20
	Jejunum	12	,,
	Ileum	19	,,
	Colon	19	,,
	Omentum	14	,,

4. Unexpected results were obtained with calcium. The plates showed a distinct increase over the control tissues (as measured by the Ca line, 4227, and the green and orange bands) in the case of the striated muscle, heart, suprarenals, gall-bladder, omentum, bowel, liver, and thyroid, from Case B. The results are shown in Table VI. The increase in the muscles is clearly seen in the plate. There would appear, therefore, to be a general increase of calcium in the tissues in haemochromatosis. The cause of this is obscure, though it is known (cf. Ramage et al. (1933)) that calcium and iron have close biological relations. A curious feature of the plates was that Ca was lower than normal in the urinary bladder, trachea, and lung, and that these tissues showed an abnormally high amount of potassium, and also a lower magnesium content than normal.

The plates were closely examined with regard to the alkali metals, and it was found that potassium in the haemochromatosis tissues was slightly higher than in the controls in the colon and duodenum and distinctly higher in the lung, trachea, bladder, suprarenals, gall-bladder, aorta, and heart.

It was about equal in the livers and lower in the brain and psoas, quadriceps, and sartorius muscles. In general the behaviour of sodium illustrated the reverse condition, being higher than the controls in the three muscles, suprarenals, gall-bladder, and colon, about equal in the brain, duodenum, heart, and liver, and lower in the lung, trachea, bladder, omentum, and aorta. There would appear, therefore, to be some disturbance in the metabolism of the alkali metals in this disease.

TABLE VI

Calcium Content of Tissues (per cent. dry tissue)

Tissue.	Control.	Case B.	Case R.	Case S.	Case McC.	Dr. Polson's case.
Quadriceps muscle	0·045	0·08	—	—	—	—
Psoas muscle	0·045	0·14	—	—	—	—
Sartorius muscle	0·05	0·11	—	—	—	0·45
Pectoralis muscle	—	—	0·08	0·12	0·04	(diaphragm)
Heart	0·08	0·25	0·22	—	0·095	0·8
Suprarenal	0·16	0·35	—	—	—	—
Gall-bladder	0·30	0·60	—	—	—	—
Omentum	0·14	0·20	—	—	—	—
Liver	0·04	0·50	0·30	0·2	0·22	0·40
Thyroid	0·20	—	0·60	—	0·0375	—
Trachea	0·35	0·33	—	—	—	—
Lung	0·40	0·30	—	—	—	—
Urinary bladder	0·18	0·12	—	—	—	—.
Aorta	0·30	0·30	—	—	—	—
Colon	0·16	0·16	—	—	0·14	—
Duodenum	0·30	0·35	—	—	—	—
Spleen	0·16	0·30	—	—	0·16	0·18
Kidney	0·10	0·35	—	—	0·14	0·25
Pancreas	0·09	0·25	—	—	0·20	0·50
Brain	0·05	0·06	—	—	—	—

Summary

There is in haemochromatosis an increase of Fe in all the tissues of the body, with the exception of the blood, brain, and colon, the two latter of which are, however, subject to individual exceptions. In certain organs the amount may be enormous, especially in the liver, pancreas, lymph glands, thyroid, salivary glands, pituitary, choroid plexuses, and heart. The increase over normal appears to be greatest in the pancreas. The somatic muscles share in these deposits of iron. The total amount of Fe deposited in the body by the time of death appears to vary from about 25 grm. to figures of the order of 45 to 50 grm.

There is a slight increase of the total sulphur in certain of the tissues, especially in the alimentary canal. This is probably related to the deposits of haemofuscin.

Spectrographic examination confirmed the results of previous chemical analyses in showing that there is an increase of copper in the liver. This increase applies to all the tissues with the exception of the kidney, small intestine, and omentum. The general order of increase is between two and three times the normal.

Certain of the tissues have an increase of Ca, which is best seen in the liver, thyroid, striated muscles, and pancreas.

Most of the tissues show disturbances in the behaviour of both Na and K, these metals usually swinging in opposite directions.
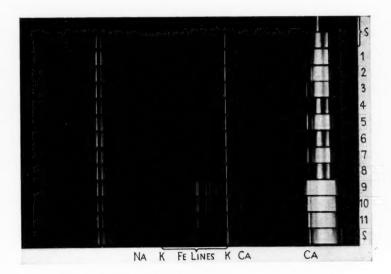
The Mn content of the liver is about one-fourth the normal. No unusual elements were met with.

REFERENCES
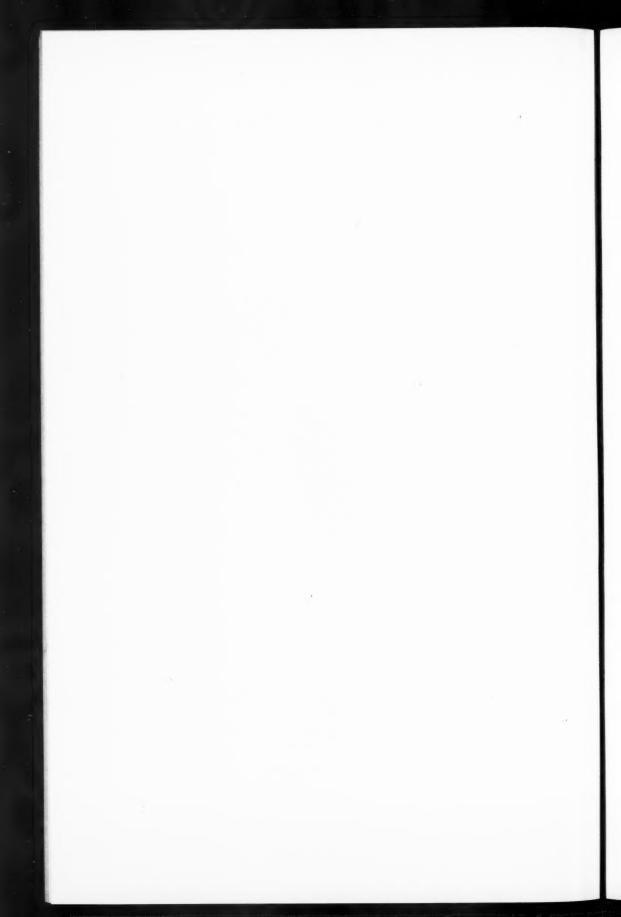
1. Sheldon, J. H., *Quart. Journ. Med.*, Oxford, 1927–8, xxl. 123.
2. Kennedy, R. P., *Journ. Biol. Chem.*, Balt., 1927, lxxiv. 385.
3. Anschütz, W., *Deutsches Arch. f. klin. Med.*, Leipz., 1897, lxii. 411.
4. Parmentier and Carrion, *Compt. rend. Soc. de biol.*, Paris, 1897, iv. Ser. x. 201.
5. Aschoff and Hess, *Berl. klin. Wchnschr.*, 1904, xli. 1231.
6. Fowell, P. H. C., *Quart. Journ. Med.*, Oxford, 1912–13, vi. 179.
7. Paviot, Chevalier, and Revol, *Semaine Méd.*, xvii. 69.
8. Rosenfeld, M., *Arch. f. exper. Path. u. Physiol.*, Leipz., 1901, xlv. 46.
9. Ramage, H., *Nature*, 1929, cxxiii. 601.
10. Herkel, W., *Ziegler's Beit. z. path. Anat.*, Jena, 1930, lxxxv. 513.
11. Schonheimer, R., and Oshima, F., *Ztschr. f. Physiol. Chem.*, Berl. and Leipz., 1929, clxxx. 249.
12. Ramage, H., et al., *Proc. Roy. Soc.*, Lond., 1933, cxiii, B. 308.
13. Ramage, H., and Sheldon, J. H., *Biochem. Journ.*, Camb., 1931, xxv. 2, 1608.

(Spectra obtained by burning 0·025 grm. dried tissue)

    S.   Standard solutions
    1.   Brain. (Haemochromatosis)
    2.   Brain. (Control)
    3.   Quadriceps muscle. (Haemochromatosis)
    4.   Quadriceps muscle. (Control)
    5.   Psoas muscle. (Haemochromatosis)
    6.   Psoas muscle. (Control)
    7.   Sartorius muscle. (Haemochromatosis)
    8.   Sartorius muscle. (Control)
    9.   Liver. (Haemochromatosis)
  10.   Lymph gland. (Haemochromatosis)
  11.   Heart. (Haemochromatosis)

THE INFLUENCE OF INFECTION ON THE ACTION OF PARATHYROID HORMONE IN MAN [1]

By G. C. LINDER

(From the Department of Pathology, University of Capetown, South Africa)

IT is well known that the presence of infection greatly increases the difficulty of treatment in diabetes. Infection may make the injection of insulin in ordinary doses quite ineffective (1), but if the infection or toxaemia can be removed a normal response to treatment will soon return. The relation of infection to the action of the other endocrine hormones has been neglected, but it seems probable that infection may influence their action in a similar way.

Linder, Harris, and Fraser (2) described two cases of tetany following thyroidectomy in which the presence of infection had a very adverse effect. In one of them 150 units (Collip) of parathyroid extract a day had almost no effect clinically or biochemically, but after sepsis had been removed and the tetany controlled the omission of 20 units was sufficient to permit the tetany to return and the serum calcium to fall 2 mg. per cent.; in the other, attacks of tonsillitis corresponded with bouts of tetany which was under control at other times. Lisser and Shepardson (3) recorded a case of tetany in which the onset of a febrile illness coincided with a fall of serum calcium from 8 to 6 mg. per cent. in spite of large doses of parathyroid—1675 units in twelve days—and recovery from the fever was followed by a rise to 12·6 mg. on a dose of 50 units a day.

The probability that the action of parathyroid hormone is frustrated by infection is indicated by such occurrences, and the present observations were made to explore the biochemical action of this hormone in other infections.

Material and Methods

Since the action of parathyroid extract varies considerably from individual to individual (4) it was necessary for each patient to furnish his own control. Choice was limited to infective states of such duration as to allow the action of the hormone to be estimated, and such severity that the patients would remain in hospital long enough to provide the control observations. Typhoid fever and pulmonary tuberculosis of slight severity were selected. The observations were made during the second week of typhoid, and the controls

[1] Received October 30, 1934.

some weeks later, just before leaving hospital. In the tuberculous cases observations obtained during a period of activity and fever were compared with those in a period of quiescence. All the patients were young adults except Case 1, aged 14.

The level of the serum calcium was determined on two or more mornings. 'Parathormone' (Eli Lilly & Co.), 20 units three times daily, was then given hypodermically for four days and the serum calcium determined on the third, fifth, and seventh mornings. The blood was taken at the same hour. The patients were not fasting. Special diets could not be used; in the tuberculosis ward the diet contained approximately 1·5 grm. Ca and 2·3 grm. P with a neutral ash, and was the same for both periods; the enteric patients received 1,500 calories, 1·0 grm. Ca, 1·2 grm. P with an ash acidity of 5 cc. N/1 acid, in the second week, and 2,700 calories, 0·9 grm. Ca, and 1·8 grm. P with an acidity of 13 during convalescence.

Additional observations were made on two patients with paraplegia whose standard metabolism was raised to + 30 by means of thyroid extract and thyroxin; their response to parathormone was obtained and compared with previous and subsequent responses at their normal metabolic level.

Results

Results in typhoid (4 cases). During the fever the initial serum calcium was reduced in three of the patients to between 8 and 9 mg. per cent. The persistence of this low figure into the period of recovery in Case 1 may be associated with the unusual length of her illness. In every case the rise in serum calcium produced by the parathyroid extract during the fever was smaller than after recovery, and in three cases the rise was very small. In Case 1 the fever was prolonged and without intermission, and it was possible to obtain two sets of observations; the response in the second was much less than in the first, and this in turn was less than the response on recovery. It appeared that the inability to respond increased as the fever continued. In Cases 1 and 2 a definite increase in the response was shown on recovery; in Case 3 a serum calcium of 13·5 mg. was reached in the recovery observations, but the net rise was not so striking because the initial serum calcium was 3·5 mg. higher than during the fever.

Results in tuberculosis (6 cases). In the febrile state the initial serum calcium was normal except in Case 9, whose condition was graver than the others; he had a progressive bronchopneumonic lesion which caused his death soon after. The parathyroid extract gave results which were quite different from those obtained in typhoid, for in every case a larger response was given during the febrile stage than on recovery. In spite of his grave state and low initial serum calcium a good response was given by Case 9.

On recovery the resting serum calcium was a little higher. The responses to parathyroid were good in Cases 5 and 6 though less than during the

active state; but in Cases 7 and 8 the responses were so small that it seems reasonable to regard them as less than normal, that is, as indicating a state of decreased reactivity to the hormone.

The results are given in Table I.

TABLE I.

Serum calcium, mg. per cent.

Case.	Dates of observation.	Control.		Day III.	Day V.	Day VII.	Increase.	Remarks.
Typhoid.								
I	10–17	8·6		9·7	13·3	10·0	4·7	Febrile
	44–51	8·4		9·0	10·3	9·9	1·9	Fever persisting
	104–111	8·7	8·7	14·8	15·8	10·0	7·1	Convalescent
II	6–14	8·4	8·2	10·2	10·0	8·2	1·9	Febrile
	29–36	9·0	9·1	13·2	10·8	8·8	4·2	Convalescent
III	7–14	8·2		8·1	9·8	9·2	1·6	Febrile
	43–50	11·8		13·4	13·5	11·3	1·7	Convalescent
IV	7–16	9·9	9·3	9·6	9·9	9·4	0·3	Febrile. Refused further injections
Tuberculosis.								
V	7–16	9·9	10·1	17·8	17·4	10·8	7·8	Febrile
	83–92	10·1	9·7	11·7	14·1	10·2	4·2	Afebrile, quiescent
VI	7–16	10·2	10·2	13·7	14·0	10·3	3·8	Febrile
	83–92	10·0	10·0	12·2	13·0	10·0	3·0	Afebrile, quiescent
VII	10–19	9·2	9·7	12·2	12·5	10·8	3·0	Febrile
	118–127	9·9	9·9	10·8	10·0	10·7	0·9	Afebrile, quiescent
VIII	9–18	9·8	10·0	11·8	14·8	11·7	4·9	Febrile
	118–127	10·6		11·0	11·2	11·0	0·6	Afebrile, quiescent
IX	10–18	8·2	8·5	14·0	14·0	11·4	5·7	Febrile, more active, died
X	12–20	9·5	9·2	12·5	12·0	9·3	3·2	Febrile, left hospital
Thyroid.								
XI	7–15	9·8	9·8	12·3	11·0	10·0	2·5	Normal state, BMR−4
	52–61	10·1	10·2	11·8	13·4	10·4	3·2	On thyroid, BMR+27
	73–81	10·8		11·8	11·0	—	1·0	Off thyroid, BMR+8
XII	45–55	10·3	10·2	11·5	13·8	10·2	3·5	40 days on thyroid. BMR +28
	62–71	9·7	9·5	11·0	11·5	9·6	1·9	Off thyroid, BMR+6

Date of observation is given in days after admission to hospital.
Day III, &c., means the third, &c., morning after the injections were begun.

Results with thyroid extract (2 cases). A bigger response was given to parathyroid by both patients when their standard metabolism was raised by thyroid than when the parathyroid was given alone before or after the period of thyroid treatment. There is a suggestion that the response to parathyroid following a period of thyroid and parathyroid was smaller than normal.

Discussion

The divergent results in typhoid and tuberculosis show that the effect of infection on the action of parathyroid hormone is not a simple matter.

There is no simple direct connexion between the degree of activity of an

endocrine gland in an individual and the response of that individual to injection of its hormone. The activity of an endocrine gland may, however, be regulated by the level of the substrate of its hormone in the blood : the secretion of insulin, for instance, is partly governed by the level of the blood sugar acting directly on the pancreas (5) and on the vagus centre (6). Similarly the activity of the parathyroid may be governed by the serum calcium, since when parathyroids are grafted hypercalcaemia does not occur, although the absence of tetany on subsequent removal of the host's parathyroids reveals the activity of the grafts (7). Responses to injected hormone will be influenced by this suppression of natural hormone secretion ; by stimulation or depression of other endocrines ; by destruction of the injected hormone ; and by alterations in the metabolic state of the subject for the substance concerned, which will depend on previous and present diet and previous treatment, particularly with the hormone in question.

It will be convenient to consider these factors in reverse order. Albright (8) and Aub (9) found that reactivity to parathyroid hormone may be lost before the mobile calcium reserves are exhausted, but in their cases the period of treatment preceding the loss of activity was much longer than the four days of the present observations. This factor is unlikely to have been the cause of the smaller response in the second series in tuberculosis, for the first period was short, the interval considerable, and the diet adequate in vitamin and calcium.

Morgan (10) concluded that the response to parathyroid is affected by the amount and ratio of calcium and phosphorus in the diet, by its acidity, and by the state of the mobile calcium reserves. The diets in the present instance contained an adequate amount of calcium and a satisfactory proportion of phosphorus. In tuberculosis the same diet was used throughout and was accompanied by cod liver oil. If Morgan's experiments in animals can be used as a guide, then the larger amount of calcium, the smaller amount of phosphorus, and the smaller acidity of the diet during the febrile period of typhoid would favour a better response then than during convalescence ; but this advantage would be readily neutralized by any considerable breakdown of tissue protein. The acidity of the diet is probably without appreciable influence for Albright (8) found that ammonium chloride acidosis increased the calcium excretion of a man taking parathormone without raising the serum calcium. In Morgan's experiments, in which a reduced response was shown, the amount given was relatively six times as great, and beyond the capacity of man to take. The early return of a normal response on recovery from typhoid without extra calcium or vitamin makes exhaustion of the calcium reserves improbable. Unfortunately local conditions do not permit the determination of calcium balances which would be desirable to confirm these points and show whether calcium excretion and absorption are normal.

Karelitz (11) and Buckley (12) attribute the lack of response to insulin in infections to its destruction by a trypsin-like ferment in the tissues ;

Himsworth (13) suggests that a kinase is necessary to activate insulin and that this may be missing.   No work of this description with parathyroid hormone has been reported.

Of the other endocrines the pituitary and the thyroid are the most likely to affect calcium metabolism in infections.

Aub (14), Tibbetts (15) and their collaborators showed that in exophthalmic goitre the excretion of calcium is greatly increased without rise in serum calcium.   They found that thyroid extract raised very slightly the serum calcium of normal persons but elevated very appreciably the low serum calcium in parathyroid tetany (9).   Their conclusion is that thyroid mobilizes large amounts of calcium from the bones which is excreted if the serum calcium oversteps a threshold set at about 8·5 mg. per cent. (16).   Hansman (17) from detailed metabolic studies concludes that patients with hyperthyroidism showing a large negative calcium balance are suffering from an associated hyperparathyroidism, and suggests, as did Aub, that the metabolic stimulus of thyroxin may increase the activity of the parathyroids.   Csépai (18) showed that in Graves' disease parathyroid extract has a greater than normal effect on the serum calcium.   Our Cases 11 and 12 showed a similar small increase in response when thyroid was given.   Histological studies of the human thyroid in infections have been recorded by Farrant (19), McCarrison (20), Cramer (21), and many others.   They agree as to the frequency of hyperplastic and degenerative changes, which Cramer interprets as indicating a state of heightened activity leading sometimes to exhaustion. In acute tuberculosis Farrant found ' complete hyperplasia' and in chronic ' colloid hyperplasia' (48 cases).   Changes were very common in infections of the intestinal group.   In these findings other authors concur.   Cole and Womack (22) found intestinal organisms particularly effective in producing experimental hyperplasia in dogs.   In typhoid Farrant found no changes (2 cases), and McCarrison states that typhoid has ' a rare but severe action' on the thyroid.   The position of typhoid is, therefore, somewhat peculiar among the intestinal infections.   To summarize—in typhoid the thyroid is usually unaffected, in tuberculosis it is overactive; thyroid secretion increases the response to parathyroid hormone to a small extent, possibly by stimulation of the parathyroid glands.

Few studies of the parathyroids in infections have been made.   Ellman (23) reported histological and clinical studies correlating increased parathyroid activity with a favourable course in pulmonary tuberculosis, but the histological standards of parathyroid activity are as yet hardly established. Obermer (24) found changes indicating extreme dysfunction in the exudative type of tuberculosis but normal histology in the proliferative type.

The probability is that the failure to elicit a normal response in typhoid is due to inactivation of the hormone, or to changes in the parathyroids or anterior pituitary.   The low initial serum calcium and the small response to the injections could be explained by partial inactivation of the natural and injected hormones.   This explanation would also fulfil the requirements

of the observations in parathyroid tetany referred to above (2, 3).   Alternatively it might be assumed that the parathyroids are working under stress and form their secretion imperfectly, and that when the stimulus to secretion is reduced by the rising serum calcium their activity falls to an abnormally low level, and consequently the rise, which is the combined effect of endogenous and exogenous hormone, is smaller than under normal circumstances. The increasing defect in response with length of illness shown in Case 1 favours the second hypothesis, for the strain on the gland would be expected to produce greater exhaustion as time went on.   It can, however, provide no explanation of the observations in tetany unless it be assumed that some active parathyroid tissue survived in these cases, which is not impossible.

The present results show that there is no inactivation of the hormone in active tuberculosis, but why does it work so well?   Has the nature of the healing of the tubercle to do with this?   The calcification of tuberculous foci appears to be an automatic sequel to the fatty changes of caseation, and akin to the calcification of other degenerate tissues.   Calcification would be facilitated by a high level of calcium and phosphorus in the serum, since the salt finally deposited is calcium phosphate (25), but that a special general reaction of calcium metabolism is involved for such a small deposit seems unlikely.   Moderate parathyroid activity leads to a diminution of serum inorganic phosphorus which would cancel to some extent the favourable effect on calcification of the higher serum calcium.

Obermer (24) and Langdon Brown (26) suggest that the thyroid, adrenal medulla, and posterior pituitary respond in emergencies and acute infections, and that in chronic infections this activity is balanced by activity of the pancreas, parathyroids, adrenal cortex and anterior pituitary which tend to promote nutrition and healing.   An explanation of the present results in tuberculosis along these lines appears possible.   The normal serum calcium at the beginning indicates at least normal parathyroid activity and the good response suggests that the natural secretion continues because of this anabolic group accentuation.   The contrast to the situation in typhoid would be complete.   Some of the credit must be given to the thyroid, for there is good evidence for its activity in tuberculosis and for the small but definite effect of this activity in increasing the response to parathyroid hormone.   The abnormally small response on recovery may be regarded as a reaction following a period of stimulation and heightened activity.

Conclusions

No general rule was found for the effect of infection on the reaction of the serum calcium to injection of parathyroid hormone.

The serum calcium was low and the response to the hormone small during typhoid fever.   A bigger response was given on recovery.

The serum calcium was normal in mild pulmonary tuberculosis.   The

response to parathyroid hormone was greater in an active than in a quiescent stage when the response was in some cases very small.
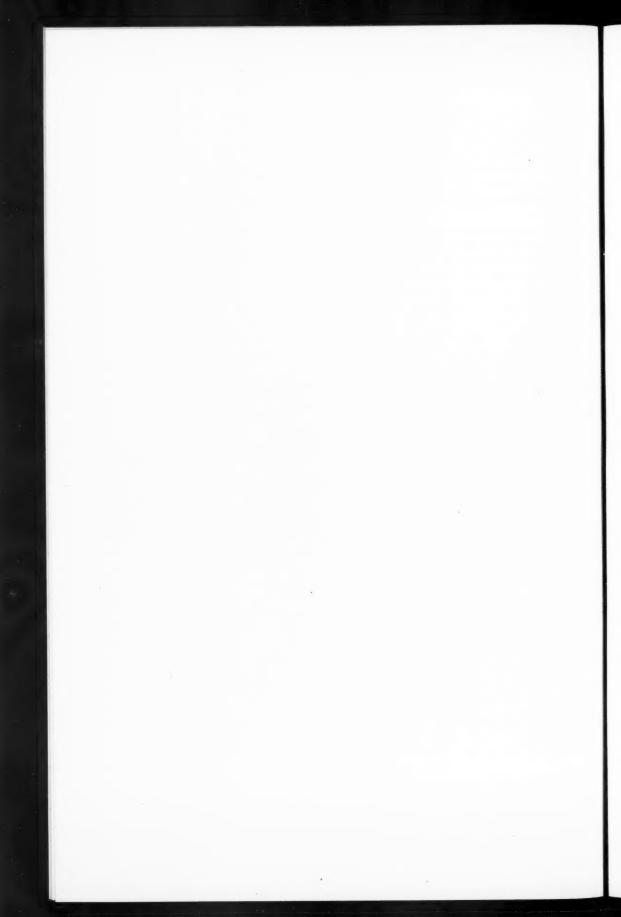
The response to parathyroid was slightly greater when the standard metabolism was raised by thyroid extract.

The factors considered most likely to be responsible for these differences were (i) inactivation of the hormone, and (ii) changes in the activity of the parathyroid, thyroid, and anterior pituitary glands.

REFERENCES

1. Graham, G., *Quart. Journ. Med.*, Oxford, 1924–5, xviii. 294.
2. Linder, G. C., Harris, C. F., and Fraser, F. R., *ibid.*, 1930–1, xxiv. 469.
3. Lisser, H., and Shepardson, H. C., *Endocrinology*, Glendale, Calif., 1929, xiii. 427.
4. Aub, J. C., *Harvey Lectures*, Balt., 1928–9, xxiv. 151.
5. Gayet, R., and Guillaumie, M., *Amer. Journ. Physiol.*, Balt., 1929, xc. 357.
6. Zuntz, E., and La Barre, J., *Compt. rend. Soc. de biol.*, Paris, 1927, xcvi. 708.
7. Lewis, J. T., and Gerschman, R., *ibid.*, 1930, ciii. 1281.
8. Albright, F., Bauer, W., Ropes, M., and Aub, J. C., *Journ. Clin. Invest.*, Balt., 1929, vii. 139.
9. Aub, J. C., Albright, F., Bauer, W., and Rossmeisl, E., *ibid.*, 1932, xi. 211.
10. Morgan, A. F., Field, J. G., Garrison, E. A., and Hills, M. J., *Amer. Journ. Physiol.*, Balt., 1933, cv. 585, 596, 608, and 621.
11. Karelitz, S., Leader, S. D., and Cohen, P., *Arch. Int. Med.*, Chicago, 1930, xlv. 690.
12. Buckley, O. B., *Brit. Journ. Exp. Path.*, Lond., 1931, xii. 13 and 1933, xiv. 57.
13. Himsworth, H. P., *Clin. Sci.*, Lond., 1933, i. 1.
14. Aub, J. C., Bauer, W., Heath, C., and Ropes, M., *Journ. Clin. Invest.*, Balt., 1929, vii. 97.
15. Tibbetts, D. M., McLean, R., and Aub, J. C., *ibid.*, 1932, xi. 1273.
16. Albright, F., and Ellsworth, R., *ibid.*, 1929, vii. 183.
17. Hansman, F. S., and Wilson, F. H., *Med. Journ. Austral.*, Glebe, N.S.W., 1934, i. 37.
18. Csépai, K., and Pelláthy, S., *Münch. med. Wchnschr.*, 1928, lxxv. 813.
19. Farrant, R., *Brit. Med. Journ.*, Lond., 1914, i. 470.
20. McCarrison, R., *The Thyroid Gland.*, Lond., 1918, 47.
21. Cramer, W., *Fever, Heat Regulation and the Thyroid-adrenal Apparatus*, Lond., 1928, 127.
22. Cole, W. H., and Womack, N. A., *Journ. Amer. Med. Assoc.*, Chicago, 1928, xc. 1274 and 1929, xcii. 453.
23. Ellman, P., *Tubercle*, Lond., 1928, ix. 162 and 1929, x. 257.
24. Obermer, E., *Proc. Roy. Soc. Med.*, Lond., 1927–8, xxi. 329.
25. Wells, H. G., *Chemical Pathology*, Philad., 1925, 487.
26. Brown, W. L., *Proc. Roy. Soc. Med.*, Lond., 1927–8, xxi. 342.

SOUNDS AND MURMURS PRODUCED BY AURICULAR SYSTOLE [1]

By CRIGHTON BRAMWELL
(From the Cardiographic Department, Manchester Royal Infirmary)

With Plates 13 to 18

A. *The Auricular Component of the First Heart-sound*

THE first heart-sound is usually attributed to ventricular systole. That auricular systole may also play a part in its production is shown by the observations described in this paper.

In a series of graphic records taken from sixteen healthy subjects, Bridgeman (4) was able to demonstrate the presence of early diastolic vibrations in thirteen and of presystolic vibrations in eleven cases. The former could be recognized clinically as the third heart-sound, but the latter were of too low intensity to reach the threshold of audibility.

That sounds may be produced by the contracting auricle was shown in 1858 by Clark, Ellis, and Shaw (5). These workers reported a remarkable case of a criminal in whom a single heart-sound was audible ninety minutes after death. On opening the chest, the ventricles were seen to be inert, but the right auricle was contracting regularly eighty times per minute.

In healthy persons with normal rhythm no distinct auricular sound is discernible, but in those types of arrhythmia in which from time to time auricular and ventricular systole occur simultaneously, the first heart-sound may be reinforced and accentuated by the auricular sound. Fig. 1 is a sound record obtained from a patient with ventricular extrasystoles. In cycles where an extrasystole happens to synchronize with an auricular contraction, the initial vibrations of the first heart-sound are of much larger amplitude than in the normal cycles. This was obvious on auscultation. Similarly in patients with complete heart-block, the intensity of the first heart-sound is apt to vary from cycle to cycle, the accentuation which occurs from time to time being due to summation of the auricular and ventricular sounds.

Again in heart-block, sounds synchronous with the isolated auricular contractions may be audible, and graphic records of these sounds have been obtained by several workers.

[1] Received December 1, 1934.

(a) *Experimental observations.* In complete heart-block the auricular sounds are generally so faint that they can only be heard with difficulty; but recently, through the kindness of my colleague Prof. Ramsbottom, I had the opportunity of making some observations on a patient suffering from Graves' disease complicated by partial heart-block. In this case, as is usual in Graves' disease, the heart-sounds were very loud. At times the block was 2 : 1 and at times 3 : 1. During the 3 : 1 periods, the auricular response to the second impulse which failed to reach the ventricle (P 3 ; Figs. 2 and 4) occurred in mid-diastole, being separated from the preceding and succeeding ventricular contractions by a considerable time interval. A loud sound always accompanied this blocked auricular contraction.

The sound was very much louder than any auricular sound which I have ever heard in a simple case of heart-block. With the help of Mr. T. S. Littler, I obtained graphic records of the heart-sounds in this case, using a Matthews' oscillograph for recording the sounds with a condenser microphone as a receiver. Since the natural frequency of both these instruments is over 10,000 per sec., it is well outside the range of frequency of even the higher harmonics of the heart-sounds. Thus we were able to obtain records which are uncontaminated by instrumental artifacts, and give a true picture not only of the time relations of the heart-sound vibrations, but also of their form. Figs. 2 and 4 are two records obtained from this case, and Figs. 3 A, B, C and D and Fig. 4 A are enlargements of the relevant portions of these records.

In Fig. 3 D, the two enlargements have been so mounted that the P wave of the blocked auricular contraction (P 3) in the lower record is synchronous with the P wave of the normal cycle (P 1) in the upper record. This serves to illustrate the time relation of the phonocardiogram to the P wave in these two cycles. It shows that the initial vibrations of the first heart-sound in the upper record bear the same relation to the P wave as does the phonocardiogram of the isolated auricular contraction in the lower record. There is also a striking similarity in wave form between the phonogram of the isolated auricular contraction in the lower record and the initial vibrations of the first heart-sound in the normal cycle of the upper record. This similarity both in time and form compels one to conclude that these two series of vibrations are due to the same cause. The sound picture in the lower record can only be produced by auricular systole. The similar series of vibrations which initiates the first heart-sound in the upper record must, therefore, also be attributed to contraction of the auricle.

In cycles where the *P-R* interval is prolonged (Fig. 3 A) the complete series of auricular vibrations can be seen; but when the *P-R* interval is of normal duration (Fig. 3 B) the final auricular vibrations are synchronous with, and obscured by, the larger initial ventricular vibrations. In normal cycles in this patient the auscultatory signs closely simulated those of mitral stenosis, but there was no other clinical or radiographic evidence of that condition.

(b) *Clinical observations.* Most workers who have studied the heart-sounds by graphic methods describe the phonogram of the first heart-sound as initiated by a series of small vibrations, some of which may be presystolic in time, preceding the upstroke of R in the electrocardiogram. In the records described above, the presystolic vibrations are of unusually large amplitude. The same is often true in simple cases of hyperthyroidism. When this is so, these vibrations give rise to an audible presystolic sound. This affords an explanation of the clinical observation, that the loud and prolonged first heart-sound characteristic of the over-acting heart in hyperthyroidism may closely simulate the first sound and presystolic murmur of early mitral stenosis. Further, I would suggest that the small presystolic vibrations which initiate the first heart-sound in records obtained from normal subjects are of a similar nature to the large initial vibrations here demonstrated in hyperthyroidism. In normal subjects these initial vibrations which constitute the auricular component of the first heart-sound are usually of such small amplitude that they fail to reach the threshold of audibility.

That an auricular component of the first heart-sound may be discernible in certain normal subjects is suggested by the following observation. In 1928 Ellis and I (2) had occasion to examine a group of 192 athletes at the Olympic Games at Amsterdam. In three Marathon runners, three long-distance runners, and three cyclists (all athletes whose particular form of sport entailed prolonged and severe exertion) the first heart-sound was unusually prolonged, and simulated remarkably closely the first sound and presystolic murmur of mitral stenosis. This peculiarity was not present in any of the thirty-four sprinters and middle-distance runners whom we examined. At the time, we were unable to offer any explanation of this observation ; but the phenomenon was so striking that we recorded it as a subject worthy of further investigation. On searching the literature, we found that a similar observation had been made by Sewell (6), who suggested that this peculiarity was due to the fact that, when the ventricle is filled at a certain rate, the reflux of the blood-current tends to bring the A-V valves into approximation. Under these circumstances, the auricle in contracting must force a channel between them, and may cause vibrations of sufficient intensity to give rise to an audible presystolic murmur. Sewell's explanation may be correct, but I am inclined to think that it is unnecessarily complicated. In the case of hyperthyroidism above referred to, the first heart-sound, in many cycles, closely resembled the accentuated first sound and presystolic murmur of mitral stenosis. The graphic records in this case indicate that the similarity is due to the unusual loudness of the presystolic auricular element of the first sound. It seems probable that, in athletes who indulge in prolonged and severe physical exertion, the auricles share in the general cardiac hypertrophy which is known to occur. If that be so, the hypertrophied auricles in these athletes might easily produce audible sound vibrations, similar to those recorded in hyperthyroidism. I have occasionally

met with a similar prolongation of the first heart-sound in elderly patients with essential hypertension, in whom there was no history of rheumatic infection and, apart from the auscultatory signs, there was nothing to suggest that they had mitral stenosis.

Fig. 8 is a phonocardiogram from a patient with congenital heart disease in whom the physical signs were a prolonged first sound, a harsh systolic murmur filling the whole of systole, and a greatly accentuated second heart-sound. The initial vibrations of the first heart-sound in this record bear a striking resemblance to the auricular component of the first heart-sound in Fig. 3 A. For purposes of comparison I have included a similar record (Fig. 9) from a patient who exhibited the typical signs of slight mitral stenosis.

It is generally believed that the principal factor in production of the first heart-sound is the sudden increase in the tension of the muscle-fibres of the ventricle. Whether the same be true of the auricular sound is more doubtful. There is the alternative possibility that this sound may, in part at least, be due, not to a muscle tone, but to vibrations set up by the blood ejected by the auricle. That such is actually the case is suggested by the time relation of the auricular phonogram to the P wave of the electrocardiogram (Fig. 3 D). This shows that the sound does not develop until auricular systole is well advanced. In this respect the auricular sound differs from the first ventricular sound, which follows closely the initial deflexions (Q R S) of the ventricular complex. On the other hand, the fact that coincidence of the auricular and ventricular contractions in patients with extrasystoles and complete heart-block increases the intensity of the first heart-sound does suggest that a muscle tone may contribute to the auricular sound. For, under these circumstances, no blood can pass through the mitral orifice, though it is possible that the impact of the blood against the closed mitral valve may produce sound vibrations.

B. *The Crescendo Murmur of Mitral Stenosis*

The presystolic vibrations which constitute the auricular component of the first heart-sound correspond in time to the presystolic vibrations which give rise to the characteristic thrill and murmur in cases of slight mitral stenosis. The two are in fact analogous, for both are probably due to eddies and vibrations set up when the size of the mitral orifice is inadequate for the quantity of blood which it has to transmit. In mitral stenosis the size of the orifice is actually diminished; whereas in hyperthyroidism the size of the orifice is normal, but the rate of blood-flow is increased. In the latter case one might say that a relative as opposed to an actual stenosis is present.

(a) *Experimental observations.* Further light on the presystolic murmur can be obtained by studying patients in whom mitral stenosis is complicated by partial heart-block. This combination enables one to observe the modi-

fications to which the murmur is subject, when the time relation of auricular to ventricular systole varies from cycle to cycle.

I had two such cases under my care a few years ago, and one of them was briefly reported at the time (1). The first patient was highly susceptible to digitalis, and partial heart-block could be easily induced by its administration. In the second case, heart-block occurred spontaneously ; and without the aid of graphic records it would have been exceedingly difficult to interpret the auscultatory signs.

At the time these two cases came under observation, I was using a rather crude technique for recording the heart-sounds. A cup receiver, placed over the region of the cardiac apex, was connected to a Frank's segment capsule by means of pressure tubing. On the edge of the capsule, was mounted a small mirror which reflected on to an electrocardiographic camera a beam of light from a Pointolite lamp. The membrane of the capsule was made from rubber solution in the manner described by Wiggers and Dean (7). An open side tube prevented rupture of the delicate membrane by the slower vibrations of pressure in the system, while permitting the more rapid sound vibrations to produce deflexions of the mirror. The defects of this method of sound registration which I have described in detail elsewhere (3) are that the sound vibrations which one is endeavouring to record are distorted by vibrations produced within the recording system. The membrane itself has a relatively low frequency of vibration (varying from about 250 to 350 per sec.), while the tube connecting the receiver to the recording capsule resonates like an organ pipe (with a frequency of 50 to 100 per sec. according to its length). Both these defects produce distortion of the records. Nevertheless, this apparatus is capable of recording accurately the time relations of the various sounds and murmurs ; and, provided that one does not require more than this, it is adequate for the purpose. Simultaneously with the sound record an electrocardiogram (Lead II) was obtained.

Fig. 5 shows a phonocardiogram taken from the first patient during a period of normal rhythm. It exhibits the typical sound-picture of fully-developed mitral stenosis. The accentuated third heart-sound (III) which is especially well shown in the first cycle, is followed by a long diastolic murmur (Diast. Mur.). This waxes and wanes and terminates in a pre-systolic crescendo element (Pre.) leading up to the succeeding first heart-sound (I).

Fig. 6 is taken from the other patient. It is more difficult to interpret, since only the first (P 1) and fourth (P 4) cycles are alike. In both these cycles the P-R interval is of normal duration ; but in the second cycle (P 2) it is prolonged, while in the third cycle (P 3) the ventricle defaults.

As in the previous record, the third heart-sound (III) in the first cycle (P 1) is followed by a long murmur. This murmur undergoes an accentuation (A 2) in association with the second auricular systole, and then dies away instead of fusing with the succeeding first heart-sound. This abnormal

behaviour is accounted for by the prolonged As-Vs interval, which in this cycle exceeds 0·3 secs.

It will be seen that the auricular accentuation of the diastolic murmur does not begin until after the end of the P wave in the electrocardiogram. In this respect it differs from the ventricular element of the first heart-sound, of which the initial large vibrations follow closely on the electrical response (R). In its time relation to the P wave the auriculo-systolic murmur closely corresponds to the auricular component of the first heart-sound in the case of hyperthyroidism described above.

In the third cycle (P 3) of this record there is no ventricular response, but the auricular murmur is of considerable intensity. In the first (P 1) and fourth (P 4) cycles, both of which follow a ventricular intermission, the presystolic auricular murmur is represented only by a few vibrations of exceedingly small amplitude; and to the ear the first sound, in cycles of this type, appeared pure, the usual crescendo murmur being absent.

(b) *Discussion*. These striking variations in intensity of the auricular murmur can be accounted for by the varying time relation of auricular to ventricular systole. When the auricle contracts early in diastole (P 3) it finds the ventricle relatively empty. Consequently it encounters little resistance in discharging its contents. A large quantity of blood is rapidly ejected through the mitral orifice and a correspondingly loud murmur accompanies the ejection. In the last cycle (P 4) of this record, on the other hand, not only does the auricular contraction occur at the end of a prolonged diastole, during which the ventricle has had ample time to fill with blood, but the ventricle has already accepted one auricular output (P 3). It is, therefore, hardly surprising that when the auricle contracts a second time (P 4), it finds the ventricle already so distended that it is hardly possible for more blood to pass through the mitral orifice. Such minute presystolic vibrations as are present in these cycles are comparable to the small pre-systolic vibrations recorded in people with healthy hearts, but are analogous to the much larger vibrations of the auriculo-systolic murmur of mitral stenosis.

Accentuation of the first heart-sound is a characteristic feature of mitral stenosis. These records appear to afford a possible explanation of that phenomenon. In the third cycle (P 3) of Fig. 6 A the auriculo-systolic murmur attains its maximal intensity about one-fifth sec. after the end of the P wave in the electrocardiogram. In the fourth cycle (P 4) the large ventricular vibrations of the first heart-sound begin to die away about one-fifth sec. after the end of the P wave. In other words, the maximal vibrations of the auricular and ventricular phonogram bear the same time relation to the electrocardiogram. This can be clearly seen in Fig. 6 C in which the two cycles P 3 and P 4 have been superimposed. The time relations of the sound and murmur in this record suggest that, in mitral stenosis, the accentuation of the first heart-sound is due to summation of the initial vibrations of the normal first sound with the terminal vibrations of the auriculo-systolic murmur.

Further evidence in support of this hypothesis is obtained from patients with mitral stenosis and auricular fibrillation. It is well known that in these cases when the heart is beating rapidly, the terminal portion of the mitral diastolic murmur often has a crescendo character which makes it indistinguishable from the auriculo-systolic murmur of the normally beating heart. This, in fact, is one of the arguments put forward by those who believe that the crescendo presystolic murmur of mitral stenosis is not produced by auricular systole. When, on the other hand, the heart is beating slowly, the later part of diastole is silent, and the murmur is diminuendo in type. Fig. 7, which is a record taken from such a case, affords a possible explanation of this anomaly. When the heart is beating slowly, as in the first three cycles of the upper and the middle two cycles of the lower record, the murmur dies away in mid-diastole and is separated from the succeeding first heart-sound by a silent interval; but when the two heart-beats follow each other in quick succession, as in other cycles, the murmur continues right up to the end of the diastole, and its terminal vibrations overlap the initial ventricular vibrations of the first heart-sound. This summation accounts for the crescendo character of the murmur in these cycles.

Summary and Conclusions

1. Records of the heart-sounds in a case of Graves' disease with partial heart-block show that the initial vibrations of the first heart-sound in normal cycles bear the same time relation to the P wave in the electro-cardiogram as do the vibrations of the auricular phonogram to the blocked auricular beats. These two series of vibrations are also similar in form.

2. When the P-R interval is prolonged the complete series of vibrations in the auricular phonogram precedes the larger vibrations of the ventricular phonogram, but when the P-R interval is of normal duration the two series of vibrations overlap.

3. These observations prove that, in this case, the initial vibrations of the first heart-sound are produced by the auricle and not by the ventricle. It is suggested that the initial vibrations seen in records obtained from normal subjects may also be attributable to auricular systole. These initial vibrations are, however, usually of such small amplitude that they fail to reach the threshold of audibility.

4. It is suggested that the similarity between the first heart-sound in hyperthyroidism, in certain athletes, in some cases of congenital heart disease and in some patients with high blood-pressure on the one hand, and the first heart-sound and presystolic murmur of mitral stenosis on the other hand, may be due to an increased velocity of the blood-flow through the mitral orifice when the auricular muscle is hypertrophied.

5. The late development of the auricular sound suggests that it is not entirely due to a muscle tone but in part at least to vibrations set up by the blood ejected by the auricle.

6. Records of heart-sounds and murmurs in two cases of mitral stenosis complicated by partial heart-block showed that the time relations of the auriculo-systolic element of the mitral murmur were strictly analogous to those of the auricular component of the first heart-sound in the case of hyperthyroidism described above.

7. There is a striking variation in the intensity of the auriculo-systolic murmur in different cycles of these records. When auricular systole occurs early in diastole the murmur is loud, but when it occurs at the end of a prolonged diastole it may be so faint that it fails to reach the threshold of audibility. Its absence in cycles following a blocked auricular beat is explained by the inability of the engorged ventricle to accept the auricular output.

8. It is suggested that summation of the terminal vibrations of the auriculo-systolic murmur and the initial vibrations produced by ventricular systole may account for the accentuation of the first heart-sound in patients with mitral stenosis.

REFERENCES

1. Bramwell, C., and Ellis, R., *Journ. Physiol.*, Lond., 1929, lxvii ; *Proc. Physiol. Soc.* xviii.
2. Bramwell, C., and Ellis, R., *Quart. Journ. Med.*, Oxford, 1930–1, xxiv. 343.
3. Bramwell, C., and Hickson, S. K., *Heart*, Lond., 1926, xiii. 129.
4. Bridgman, E. W., *Arch. Int. Med.*, Chicago, 1914, xiv. 475,
5. Clark, Ellis, and Shaw, *Boston Med. Surg. Journ.*, 1858, v. 480.
6. Sewell, H., *Amer. Journ. Med. Sci.*, Philad., 1909, N.S. cxxxviii. 10.
7. Wiggers, C., and Dean, A., *ibid.*, 1917, cliii. 666.

DESCRIPTION OF PLATES

FIG. 1.   Synchronous electrocardiogram and optical phonocardiogram from a patient with frequent ventricular extrasystoles (Ex.).   In cycles in which auricular and ventricular systole coincide, the vibrations of the first heart-sound are of increased amplitude, the ventricular and auricular sounds being superimposed.   1 = first heart-sound, 2 = second heart-sound.

FIG. 2.   Synchronous electrocardiogram (uncalibrated) and phonocardiogram (recorded by Matthews' oscillograph and condenser microphone), from a patient with Graves' disease and varying 2 : 1, 3 : 1 A-V block.   Time intervals 0·2 secs.

FIG. 3 A.   Enlargement of section A (Fig. 2) showing complete auricular phonogram preceding first sound of ventricular phonogram in cycle in which *P-R* interval is prolonged.   Auric = auricular, and Ventric = ventricular component of the first heart sound.

FIG. 3 B.   Enlargement of section B in Fig. 2 showing overlapping of auricular and ventricular phonograms in cycle in which *P-R* interval is of normal duration.

FIG. 3 C.   Enlargement of section C of Fig. 2 showing isolated auricular phonogram. Note similarity in wave form of auricular phonograms in these three records.

FIG. 3 D (i) and (ii).   Two similar enlargements of the section D of Fig. 2.   The T wave in the electrocardiogram is continuous with the succeeding P wave (P 2).   The lower enlargement has been mounted to make P 3 synchronous with P 1.   This shows that the time interval between the upstroke of P 1 and the initial vibrations of the first heart-sound (in Fig. 3 D i) is the same as that between the upstroke of P 3 and the vibrations of the auricular sound (in Fig. 3 D ii).   The second vertical line is intended to illustrate the time relation of the upstroke of R to the auricular sound vibrations.

FIG. 4.   Record similar to Fig. 2 but with sound-recording apparatus rendered rather more sensitive.   Note similarity in form between the isolated auricular phonogram P 3 and initial vibrations of succeeding first heart-sound.

FIG. 4 A.   Enlargement of section A of Fig. 4.

FIG. 5.   Electrocardiogram and optical phonocardiogram (enlarged) from a patient with mitral stenosis and normal rhythm.   I. first heart-sound.   II. second heart-sound. III. third heart-sound.   Diast. Mur. = Diastolic murmur.   Pre. = crescendo presystolic murmur.

FIG. 6 A.   Electrocardiogram and optical phonocardiogram (enlarged) from a patient with mitral stenosis and partial A-V block.

FIG. 6 B.   Outline drawing of Fig. 6 A.   I. first heart-sound.   II. second heart-sound. III. third heart-sound.   Black rectangles in diagram of sound record correspond in time to P waves in electrocardiogram.

FIG. 6 C.   Diagram taken from Fig. 6.   The phonograms of the third cycle P 3 and the fourth cycle P 4 are superimposed, so that P 3 coincides with P 4.   The light outline represents the isolated auricular murmur in cycle P 3, the heavy outline the first heart-sound in cycle P 4.   The two are seen to overlap, thus accounting for the accentuation of the first heart-sound which is typical of mitral stenosis, the initial vibrations of the normal first heart-sound being supplemented by the final vibrations of the auriculo-systolic murmur.

FIG. 7.   Optical phonocardiograms from a patient with mitral stenosis and auricular fibrillation to illustrate the silent interval which follows the murmur when diastole is prolonged, and the continuance of the murmur throughout diastole when two heart-beats follow one another in quick succession.

FIG. 8.   Phonocardiogram recorded by Matthews' oscillograph and condenser microphone from a patient with congenital heart disease.   Note similarity of wave form of auricular component (Au.) of first heart-sound (1) with that in Figs. 3 and 4. S. m. = systolic murmur.   2 = second heart-sound.

FIG. 9.   Phonocardiogram recorded by Matthews' oscillograph and condenser microphone, from a patient with slight mitral stenosis.   Pre = presystolic murmur.   1 = first heart-sound.   2 = second heart-sound.

FIG. 1

FIG. 2

FIG. 3 A

auric   ventric
1st heart sound   2nd sound

FIG. 3 B

FIG. 3 C

1st heart   2nd sound
sound

auricular
sound

(i)

(ii)

FIG. 3 D

FIG. 4

FIG. 4 A

Fig. 5
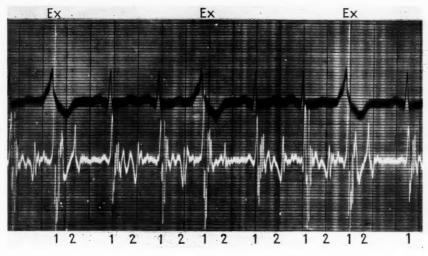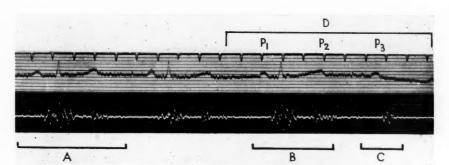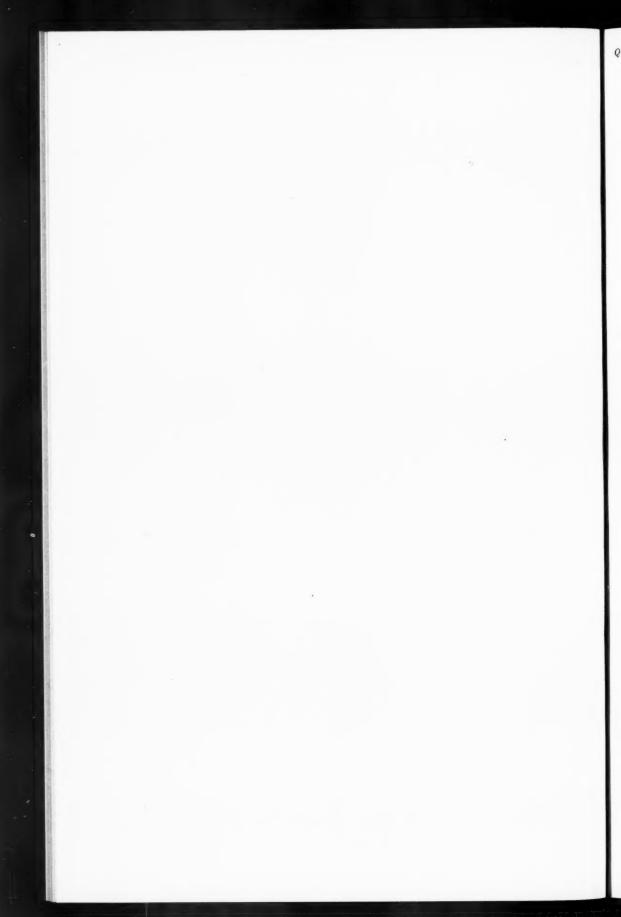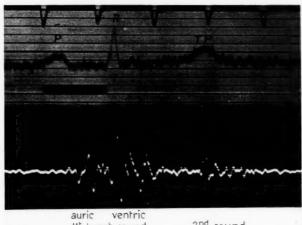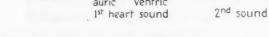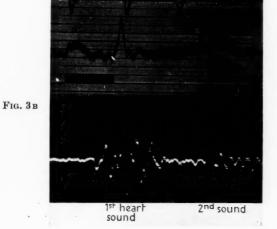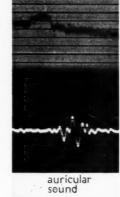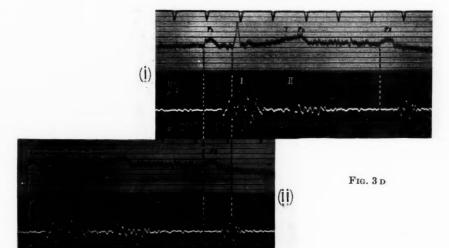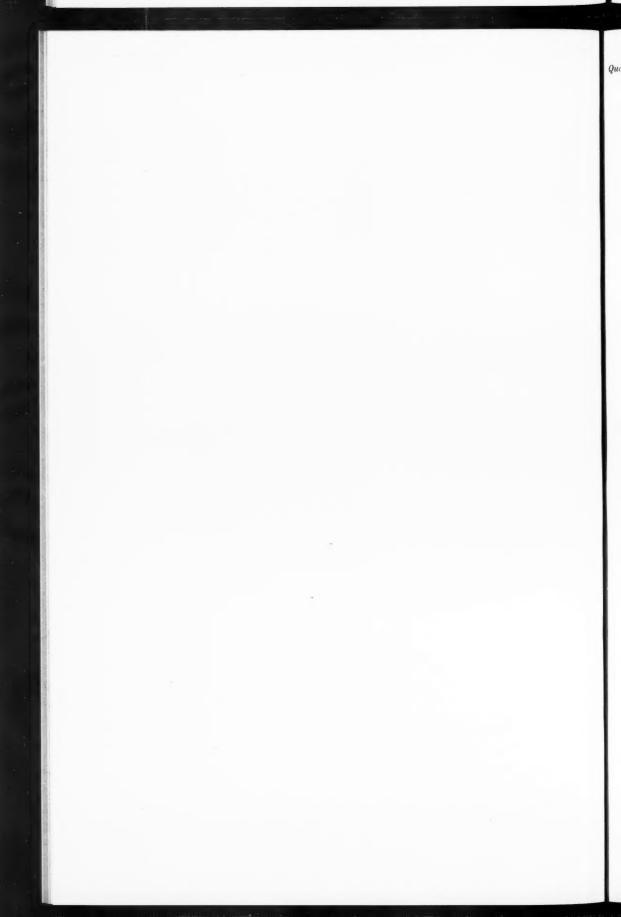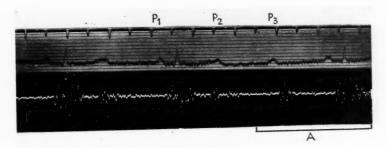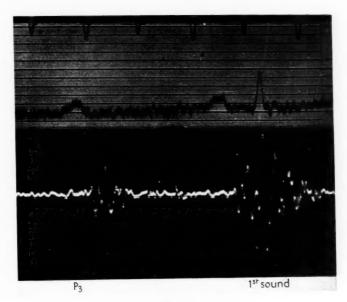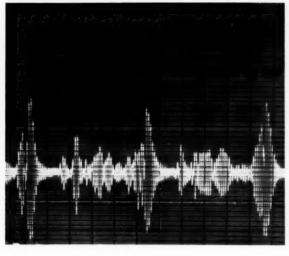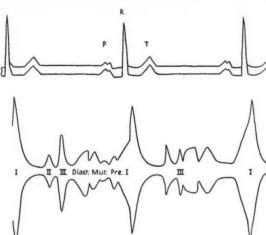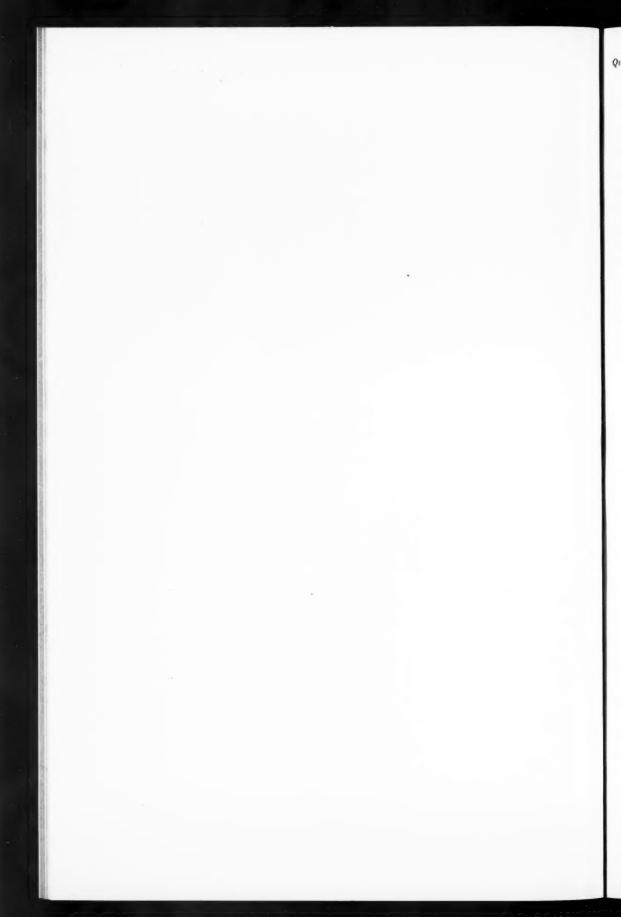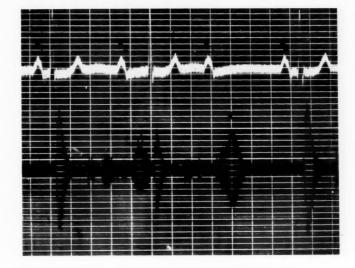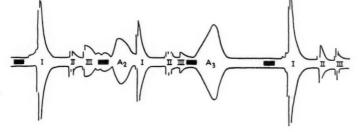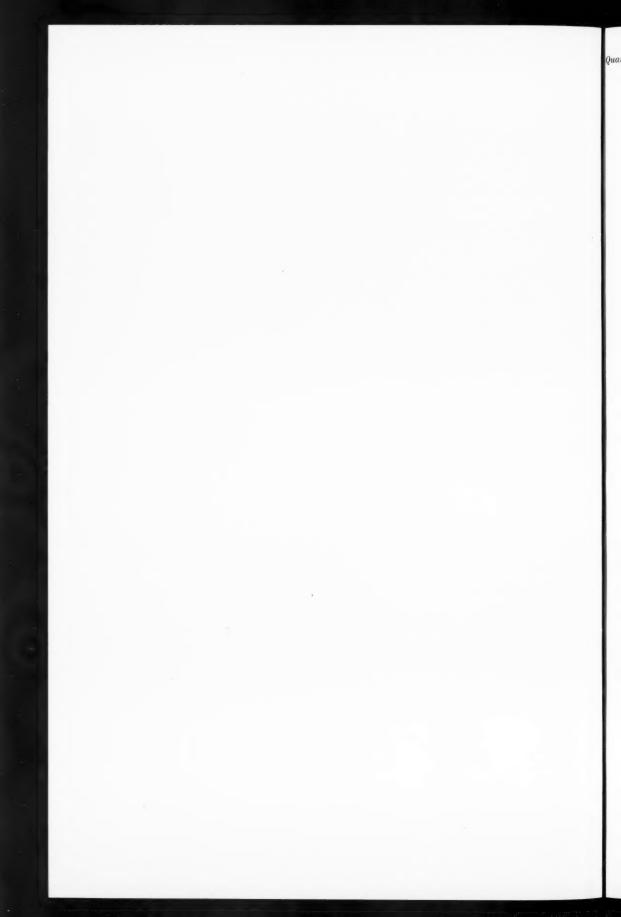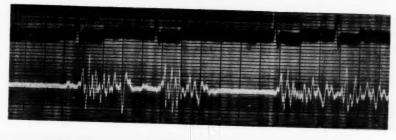
Fig. 6
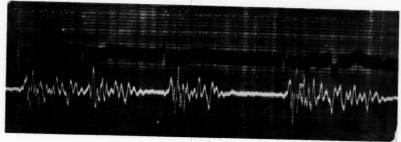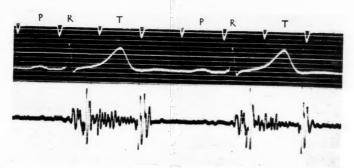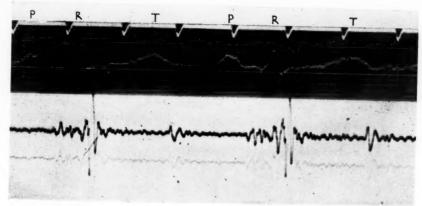
FIG. 7

Au. 1   S.m. 2

FIG. 8
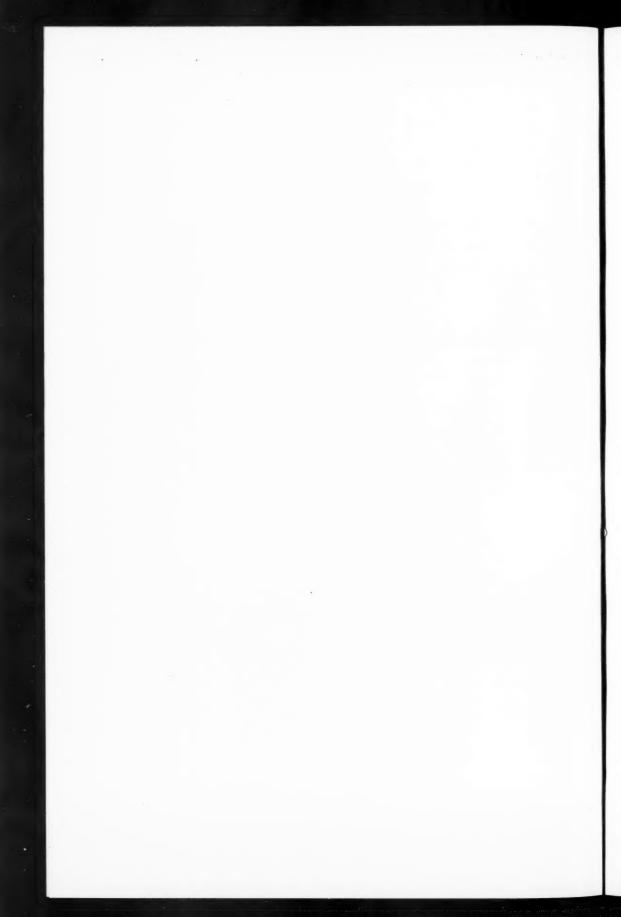
Pre 1   2   Pre 1   2

FIG. 9

GALLOP RHYTHM [1]

By CRIGHTON BRAMWELL

(From the Cardiographic Department, Manchester Royal Infirmary)

With Plates 19 to 21

GALLOP rhythm is the name applied to a disorder of the heart's mechanism in which three instead of two sounds accompany each cardiac cycle. This sign has been described as ' the cry of the heart for help '. It is a sure indication that the last reserves have been called up, and that the heart is struggling against desperate odds. Although the grave significance of gallop has been recognized by clinicians for more than half a century, there is as yet no general agreement regarding the way in which this important sign is produced.

My purpose in this paper is to review the clinical findings and after-histories in a consecutive series of sixty-two cases in which this sign was present ; to consider the significance of these findings with special reference to prognosis ; and to put forward a hypothesis regarding the mechanism of production of gallop rhythm.

I. *Types of Triple Rhythm*

In the past much confusion has arisen from failure to distinguish between gallop and other types of triple rhythm (i.e. other conditions in which three instead of two heart-sounds accompany each cardiac cycle). Many writers fail to differentiate between gallop and accentuation of the normal third heart-sound, while others confound with gallop the split sounds due to asynchronous closure of the aortic and pulmonary valves. Neither of these signs is of the same grave significance as true gallop, and it is therefore important that they should be clearly distinguished from it. Just as the label ' angina pectoris ' should be attached only to those cases of cardiac pain in which there is danger of sudden death, so it is desirable that the term ' gallop ' should be reserved for that type of triple rhythm in which the heart is embarrassed. To include under the title of ' gallop ', simple accentuation of the physiological third heart-sound, or split sounds, is to confuse the issue, and until these phenomena are clearly distinguished from gallop, no progress is possible.

[1] Received December 1, 1934.

(a) *Split heart-sounds.*   Potain (10) clearly differentiated between gallop and split sounds.   He pointed out that in split sounds, the two components are of the same quality and pitch, and are separated from one another by only a very short time interval; whereas the gallop sound is dull in quality, it is accompanied by a palpable shock, and is separated by a much longer time interval from the two normal sounds.   The gallop sound is usually best heard between the cardiac apex and the sternum, whereas split sounds are heard only over the base of the heart.

Split sounds are believed to be due to asynchronous closure of the aortic and pulmonary valves.   Katz (6) showed experimentally, in dogs, that the contraction of the right and left ventricles is not absolutely synchronous: and it is hardly surprising that this normal asynchronism should be increased under pathological conditions, when, as is frequently the case, the brunt of the strain falls on one or other ventricle.

(b) *The physiological third heart-sound.*   The difficulty in defining the term gallop is emphasized in a recent paper by Wolferth and Margolies (13).   Their paper deals with gallop rhythm and the physiological third heart-sound. These workers state that they are unable to find any obvious means of differentiating these two phenomena.   They apply the term ' gallop rhythm ' to those cases in which there is, and ' physiological third heart-sound ' to those in which there is not, any associated abnormality of cardiac function. They admit that this classification is arbitrary and unsatisfactory.   It is more than that, it is misleading.   The clinical and prognostic significance of the gallop sound is essentially different from that of the ' physiological ' third heart-sound, no matter whether the additional heart-sound be or be not associated with evidence of deranged cardiac function.

The features to which I attach most importance in differentiating these two phenomena are as follows: (1) Gallop is generally easily palpable as well as audible, the impression received by the hand being analogous to that received by the ear.   It is only in emphysematous and obese subjects that this confirmatory sign is absent.   The accessory sound in gallop is often only a dull thud, and the abnormality of rhythm is sometimes even more obvious on palpation than on auscultation.   As the French school of cardiologists point out, gallop is most easily detected by applying the ear directly to the chest wall, since, by so doing, not only the sound but also the associated impulse is appreciated.   For the same reason, gallop is less likely to be missed with a rigid monaural than with a binaural stethoscope. The physiological third heart-sound, on the other hand, though it may be accompanied by a slight shock, which is perceptible on palpation, is never associated with a modification in the character of the cardiac impulse such as occurs in gallop.   The normal cardiac impulse is a single thrust, but the gallop impulse is a double wave, the two components of which are similar to one another.   This gives to the hand the impression that the chest wall is not merely being pushed out by the turgid apex of the ventricle, but that it is being thrown into oscillation.   (2) The three sounds in gallop

are almost evenly spaced, whereas the physiological third heart-sound is obviously more closely related to the preceding second sound than to the succeeding first heart-sound. (3) True gallop never occurs unless the heart-rate is rapid.

The mechanism of production of the physiological third heart-sound will be considered later.

(c) *The third sound in mitral stenosis.* In patients with mitral stenosis, three heart-sounds are often audible. The additional sound in these cases is variously referred to as ' a reduplication of the second sound ' an ' accentuated third heart-sound ' or ' the opening snap of the mitral valve '. The difference is merely one of nomenclature ; all three descriptions refer to the same phenomenon. The commonness of this sign, and the fact that I have never met with true gallop in a patient with mitral stenosis, lead me to believe that this type of triple rhythm is quite distinct from gallop. Later, when considering the mechanism of production of gallop rhythm, I shall refer to the reasons why one would not expect it to occur in association with mitral stenosis.

(d) *Proto-diastolic gallop.* In the past it has been customary to describe two types of gallop rhythm—a ' proto-diastolic gallop ' in which the additional sound occurs early in diastole, and is more closely related in time to the preceding second than to the succeeding first heart-sound, and a ' presystolic gallop ' in which the additional sound occurs during auricular systole. The term ' proto-diastolic gallop ' is a bad one, for two reasons. First, because the epithet ' proto-diastolic ' is applied by physiologists to that phase of the cardiac cycle which immediately precedes the closure of the semilunar valves, whereas the gallop sound occurs after the opening of the mitral valve. Secondly, when the heart-rate is rapid, diastole is curtailed to such an extent that auricular systole follows immediately on ventricular systole and occupies early diastole. Under these circumstances presystole and early diastole are one and the same thing, and presystolic gallop becomes ' proto-diastolic' in time. The term ' summation gallop ' has been suggested by Wolferth and Margolies (13) to describe that type of gallop in which the presystolic and early diastolic sounds are superimposed ; but, for reasons which will be given later, this addition to the nomenclature appears to me to be unnecessary.

My own observations lead me to believe that the so-called ' proto-diastolic gallop ' is nothing more nor less than accentuation of the physiological third heart-sound. If this view be correct, it is clearly desirable to dispense with the term ' proto-diastolic gallop ' and to reserve the name ' gallop ' for the presystolic variety. The latter is a distinct clinical entity, and carries a grave significance in prognosis, which is not attached to any other type of triple rhythm.

II. *Clinical Features*

In a consecutive series of 1,353 cardiac cases (i.e. cases sent to me either on account of heart disease, or of symptoms believed to be due to heart disease) seen in private practice during the three years 1930–32, I noted the presence of gallop rhythm in sixty-three patients. Of these one has been lost sight of, and in the following analysis of the clinical features I shall deal only with the other sixty-two, of whom fifty-two are dead, and ten were living in July 1934 (i.e. eighteen months or more after they first came under observation).

On studying this group of cases, one's attention is arrested by certain out-standing features, namely : (1) the very high mortality ; (2) the rarity of the inflammatory as compared with the degenerative types of heart disease ; (3) the frequency of congestive heart failure, anginal pain, and cardiac asthma ; and (4) the invariable presence of tachycardia.

(a) *Aetiology.*   In this series of sixty-two patients, eight only were under 40 years of age (Table I).

TABLE I

Age Incidence

	Living.	Dead.	Total.
Under 40	—	8	8
40–49	2	12	14
50–59	5	14	19
60–69	3	14	17
Over 69	—	4	4
	10	52	62

In other words, the sign occurred most frequently during the degenerative period of life. Of the eight young subjects, six were suffering from acute endocarditis, one from hypertension with sub-acute nephritis, and one from spinal caries. All eight are dead.

It is well known that, in young persons, gallop rhythm not infrequently occurs in association with diphtheria and other acute infections of the myocardium.   In cardiological practice, however, one rarely has the oppor-tunity of seeing these diseases : and I have no doubt that this group of cases would figure much more prominently in the practice of a specialist in children's diseases or in the infectious fevers.   The present series of sixty-two cases cannot, therefore, be regarded as a perfect sample, either from the pathological standpoint or for the age incidence.

Twenty-five of my patients who had a systolic blood-pressure of over 160 mm. (Table II) were suffering either from essential hypertension, chronic Bright's disease or general arteriosclerosis.   Nine had acute symptoms of myocardial infarction following coronary occlusion, and eight others gave a history of anginal symptoms with a rapid deterioration in exercise tolerance suggestive of advanced and progressive coronary lesions. Six, to whom I have referred above, had acute endocarditis, and the remaining fourteen were

suffering from heart failure attributable to various conditions. This last group included cardio-aortic syphilis (3 cases), emphysema (3 cases), heart failure, for which I was unable to find the cause (3 cases), spinal caries (2 cases), post-operative collapse (2 cases, in one of which there was a history of Graves' disease), and congenital heart disease aggravated by alcoholic excess (1 case).

TABLE II

Systolic blood-pressure.	Hypertension and chronic Bright's disease.	Coronary arterio-sclerosis.	Acute infections.	Miscellaneous.	Total.
Over 200	17	1	—	—	18
165–200	8	4	1	4	17
135–160	—	2	—	7	9
under 135	—	10	5	3	18
	25	17	6	14	62

(b) *Signs and symptoms.* The symptoms of which these patients chiefly complained were (i) dyspnoea on exertion (in 17 cases), (ii) cardiac asthma (in 12 cases), (iii) angina of effort (in 11 cases), and (iv) anginal pain occurring at rest (in 12 cases).

Twenty-six patients exhibited signs of congestive heart failure. Of these, twenty-five had normal sinus rhythm, while one in whom no electro-cardiogram was obtained had irregular heart action. Clinically it was not possible to be certain whether the arrhythmia in this case was attributable to frequent extrasystoles or to auricular fibrillation. The former seems the more probable, in view of the fact that in only one of the other sixty-one cases was the heart's action grossly irregular. The heart-rate in that case was 104, but again, unfortunately, no electrocardiogram was obtained.

The presence of congestive heart failure in association with normal rhythm in twenty-five, and probably in all the twenty-six, cases in this series calls for explanation, for congestive heart failure is notoriously much more common in patients with auricular fibrillation than in those with normal rhythm. The explanation, as I shall show later, appears to be that contraction of the auricle plays an essential part in the production of gallop rhythm, and that true gallop therefore cannot occur in association with auricular fibrillation. In fact, when the auricles fibrillate, gallop rhythm, if it had previously been present, disappears. This fact has been noted by other workers.

This group of cases illustrates in a striking way the two types of heart failure. In some patients, myocardial insufficiency shows itself by dyspnoea, venous engorgement, and oedema, while in others it does so by anginal pain. These two manifestations of heart failure rarely appear together. They seem to be mutually exclusive. The patient with venous engorgement may have discomfort, but he rarely complains of actual pain, and the patient with pain in the chest on exertion, who subsequently develops venous engorgement, may become immune from further anginal attacks. In this series of sixty-two cases, twenty-one of the patients with venous engorgement had never suffered from cardiac pain. Conversely, nineteen patients

whose chief complaint was pain of an anginal distribution, occurring either
on exertion or at rest, did not exhibit any evidence of venous engorgement.
Thus whereas there were forty patients in whom one or other of these mani-
festations of heart failure was present, both had been present in only five
cases, and all five were suffering from myocardial infarction following
coronary occlusion.

It is customary to apply the term ' heart failure ' only to those patients
who have venous engorgement and oedema.   But since ' heart failure '
clearly means failure of the heart to meet its liabilities, I consider that the
term is equally applicable to the anginal type of case in which the patient's
activities are limited not by dyspnoea, but by pain.   The pain in angina of
effort, as well as in the closely related condition coronary occlusion, is due to
a shortage in the supply of oxygen to the heart muscle.   I would therefore
suggest that in addition to the ' congestive ' type of heart failure associated
with venous engorgement it would be logical to speak also of an ' ischaemic '
type of heart failure, attributable to myocardial ischaemia.

Tachycardia is a constant finding in true gallop rhythm.   In fifty of the
sixty-two cases in my series, the resting heart-rate was between 90 and 120
per minute.   There were ten patients whose heart-rate was over 120.   All
ten are dead.   Thus a moderate degree of tachycardia appears to be a factor
favourable to the development of gallop rhythm.   The significance of this
observation will appear later.

Electrocardiograms were obtained in thirty-three cases.   Seven of these
exhibited bundle branch-block.   In one electrocardiogram the P-R interval
was prolonged, but this abnormality was not present in any of the other
thirty-two records. Apart from the usual T wave changes in the patients with
coronary occlusion, there were no features in the electrocardiograms which
call for special mention.

In six of the patients in this series gallop was not present when I first
examined them, but developed at a later date.   Table III summarizes the
clinical findings before and after the appearance of gallop in these cases.

TABLE III

Case.	Age.	Date.	Gallop.	Pulse.	B.P.	Diagnosis.
I	56	9.10.30	—	90	195/110	Essential hypertension with
		24.10.32	+	100	105/90	coronary occlusion
II	68	23.10.30	—	88	235/115	Essential hypertension
		2.8.32	+	106	230/130	
III	37	13.11.30	—	100	135/65	Infective endocarditis
		9.12.30	+	94	120/40	
IV	48	20.5.31	—	62	215/125	Chronic Bright's disease
		7.11.32	+	98	210/140	
V	71	29.6.31	—	80	160/90	Coronary occlusion
		23.7.31	+	112	120/80	
VI	68	9.10.32	—	84	230/130	Essential hypertension
		18.11.32	+	110	210/130	
		2.12.32	+	100	210/130	

In Cases I and V the appearance of gallop followed an acute myocardial
infarction.   In the former the blood-pressure had dropped from 195/110 to

105/90, and in the latter from 160/90 to 120/80.   Case III was a patient with infective endocarditis and aortic incompetence. His pressure fell from 135/65 to 120/40 as the heart failed.   Cases II, IV, and VI all had a very high blood-pressure, and the appearance of gallop was associated with progressive cardiac failure.

In all these patients, with the exception of Case III, the pulse-rate was higher when gallop developed than it had been prior to its appearance.

One other case calls for special mention. A man of 41 suffering from chronic Bright's disease consulted me in October 1932 on account of intense dyspnoea after a stiff climb to the moors. He had typical gallop rhythm, his pulse-rate was 128, and his blood-pressure 170/90. With ten days rest in bed the pulse-rate fell to 92, the pressure rose to 190/105, and the gallop completely disappeared. I saw him again three months later, during a slight febrile attack. The pulse was 104, the pressure was 170/90, and there was still no sign of gallop. I next saw him in March 1933, following an attack of cardiac asthma. He then had auricular fibrillation which persisted till he died in July. The pressure still remained in the neighbour-hood of 170/100, but there was no sign of gallop. I saw him again at the end of June, when he was troubled by attacks of nocturnal dyspnoea. His liver was enlarged, and the blood-pressure was in the neighbourhood of 170/130. He rallied from time to time, but on the whole his condition steadily deteriorated. During the last three weeks of his life I saw him on several occasions, but, in spite of the fact that the heart was pro-gressively failing, there was never any suspicion of gallop rhythm. Its absence can, I think, only be accounted for by the onset of fibrillation. All the other factors which would have favoured its recurrence were present.

(c) *Prognosis.* The grave significance of gallop rhythm is sufficiently indicated by the fact that of these sixty-two patients only fifteen lived for more than eighteen months after the sign was first noted, and of these five have since died.   Table IV shows the duration of life.

TABLE IV

Less than 1 month	16
1–6 months	19
6–18 months	12
More than 18 months (now dead)	5
More than 18 months (still living)	10
	—
	62

Of the fifteen patients who lived for more than eighteen months, seven were suffering from essential hypertension, four from coronary occlusion or advanced coronary disease, two from post-operative collapse, one from congestive heart failure associated with emphysema, and one from a con-genital heart lesion aggravated by alcoholic excess.

When one compares the group of fifteen patients who survived for more than eighteen months after gallop was first noted with the forty-seven patients who died within that period, one is struck by the fact that all the

survivors were between the ages of forty-seven and sixty-eight. It is not
surprising that the five patients over that age should have died, but it is
rather surprising that none of the sixteen patients under 47 years of age
should have survived (Table V).

TABLE V

	Lived for more 18 months.	Died within 18 months.	Total.
Under 47	—	16	16
47–49	2	4	6
50–59	6	13	19
60–68	7	9	16
Over 68	—	5	5
	15	47	62

If one pursues the inquiry further, one finds that not merely did all these
young patients die within eighteen months, but only three of them survived
for more than two months after gallop was first detected. Five were
suffering from chronic Bright's disease, five from acute endocarditis, and
two from congestive heart failure associated with spinal caries, one had
essential hypertension, one had coronary embolism, one cardio-aortic syphilis,
and there was one in whom I was unable to determine the cause of the
heart failure. Acute endocarditis and chronic Bright's disease are the out-
standing aetiological factors in this group. These conditions account for
ten of the sixteen deaths amongst the younger patients.

Contrast with this group the fifteen older patients who survived for more
than eighteen months, eleven of whom were suffering from either essential
hypertension or coronary arteriosclerosis. These are more chronic diseases,
and that appears to be the explanation of the rather surprising fact that
the immediate prognosis in patients with gallop rhythm is rather less grave
in the sixth and seventh decades than during the earlier period of life.

Five of the seven patients with bundle branch-block lived for more than
eighteen months, though four of them have since died. One would not
have expected these patients to live so long, for bundle branch-block in
patients with symptoms of cardiac insufficiency is a sign of ill omen, and
when combined with gallop rhythm, one would have anticipated that it
would have added still further to the gravity of the prognosis.

III.   *The Physical Basis of Gallop Rhythm*

The clinical observations reported in the first part of this paper serve to
eliminate two disorders of the heart's mechanism which have in the past
been regarded as possible causes of gallop rhythm, namely—partial heart-
block and bundle branch-block.

(a) *Relation of gallop to* A-V *block and bundle branch-block.*   Lewis (8) and
other workers have suggested that prolongation of the As-Vs interval might
give rise to gallop.   It is true that when the As-Vs interval is prolonged the

auricular component of the first heart-sound may be audible as a distinct entity. This was so in a case of hyperthyroidism which I have described in my previous paper (1). Under these circumstances three sounds instead of two accompany each cardiac cycle. Triple rhythm is present; but this type of triple rhythm is quite distinct from true gallop. In only one of the thirty-three cases in my series, in which I was able to obtain an electrocardiogram, was the *P-R* interval prolonged.

That bundle branch-block might be the underlying mechanism responsible for the appearance of gallop is, at first sight, a very plausible suggestion. These two disorders not infrequently occur together. The association, however, is not sufficiently constant to establish any *causal* relationship between them. In my thirty-three electrocardiograms from patients with gallop there were only seven examples of bundle branch-block. As a control, one may take the whole group of 1,353 patients amongst whom those sixty-two cases of gallop occurred. The total number of electrocardiograms in the whole series showing complete bundle branch-block was sixteen. Thus one can say that neither did the majority of patients with gallop rhythm exhibit bundle branch-block, nor did the majority of those with bundle branch-block exhibit gallop rhythm. One has to admit that only thirty-three of the sixty-two patients with gallop were examined electrocardiographically, and that the incidence of bundle branch-block might have been higher amongst the other twenty-nine patients. This criticism, however, would be purely speculative: there is no evidence to support it.

On the other hand, it is not surprising that many patients with gallop rhythm should also have bundle branch-block. Both are signs of grave myocardial damage, and both are therefore likely to occur in patients with heart failure secondary to degenerative lesions of the myocardium. In twelve of the sixteen cases of bundle branch-block in my whole series, the aetiological diagnosis was either arteriosclerosis or essential hypertension. The same applies to *pulsus alternans*, which often occurs in association with either gallop rhythm or bundle branch-block. No one of these three signs can be regarded as responsible for the production of either of the other two. They merely happen to occur together, since they are all manifestations of grave myocardial lesions.

Lewis (7 and 8) has published a sound record obtained from a patient with bundle branch-block who also exhibited gallop rhythm, and Fig. 2 shows a very similar record obtained from one of my own patients. As Lewis points out, the reduplication of the first sound in his case cannot be attributed to asynchronous contraction of the ventricles since the first element of the reduplication commences in presystole. He does suggest, however, that the two sounds are produced in a similar way, namely, by closure of the A-V valves. He bases his argument on the similarity in wave-form of the two elements of the reduplication. I would suggest that there is another possible explanation of the similarity between the presystolic and systolic vibrations in both Lewis's record and my own. Both of us were, at that time, using

recording devices in which the receiver on the chest was connected to the recording instrument by a long piece of rubber tubing. Hickson and I (2) showed that a tube of a metre in length tends to resonate like an organ pipe with a frequency of about 70 per sec., and so distorts the sound vibrations which one is endeavouring to record. The vibrations in both Lewis's and my own records are of about the frequency which one would expect in a tube of 4 to 6 feet long.

Maurice Campbell (3) reported an extremely interesting case which has an important bearing on this problem. In his patient, when first seen, gallop rhythm was associated with bundle branch-block. Nine months later, the electrocardiogram showed a normal QRS complex, and gallop rhythm was no longer present. These findings might be interpreted to mean that, in this patient, the bundle branch-block was responsible for the gallop rhythm. There is, however, an alternative explanation. When bundle branch-block was present, the heart-rate was in the neighbourhood of 100 per minute, while with normal mechanism it had fallen to about 75. My observations show that some degree of tachycardia is a *sine qua non* to the development of gallop rhythm, and I believe that the disappearance of gallop in Campbell's case was due to the disappearance, not of the bundle branch-block, but of tachycardia. I have repeatedly noticed in my own patients with gallop rhythm, that the gallop disappeared when the heart slowed down.

(b) *Relation of gallop rhythm to auricular systole.* If gallop rhythm is not attributable either to prolongation of the As-Vs interval, or to bundle branch-block, some alternative explanation of its presence must be sought. Whatever explanation is suggested must account for the facts that gallop-rhythm only develops when heart failure of one or other type is present or imminent, that it is invariably associated with some degree of tachycardia, and that it does not occur in patients with auricular fibrillation. This last observation suggests that contraction of the auricle is essential to the production of gallop.

The hypothesis that the additional sound in gallop [2] is produced by auricular systole was first formulated by Charcelay (4) nearly a hundred years ago. He pointed out that the gallop sound was synchronous with auricular systole, and that hypertrophy of the auricle was often found at autopsy in cases where gallop had been present during life. Graphic records point to the same conclusion. Mond and Oppenheimer (9) showed that the supernumerary heart-sound in gallop is always closely related in time to the P wave of the electrocardiogram, and that the sound disappears when the auricles fibrillate. This observation has been confirmed by other workers.

Fig. 3, which is one of many similar records taken from one of my own patients, serves to illustrate this point. The vibrations of the first heart-sound (1) correspond in time to the R wave of the electrocardiogram, those

---

[2] Charcelay did not use the term 'gallop', but his clinical description clearly applies to this type of triple rhythm.

of the second sound (2) to the T wave, and those of the gallop sound (G) to the succeeding P wave.

The nature of the sound produced by auricular systole has been fully considered in my previous paper (1). It remains to inquire whether this sound may be accentuated and modified in such a way as to give rise to gallop.

(c) *The filling of the ventricle.* In discussing the clinical diagnosis of gallop rhythm I pointed out that the gallop sound is generally accompanied by a palpable diastolic impulse. The time relations of this impulse suggest that it is produced by the emptying of the auricle into the ventricle. Observations on animals show that, in health, ventricular filling occurs chiefly in early diastole, and that the contribution made by auricular systole to the filling of the ventricle is relatively small.

When the heart is beating slowly, ventricular diastole may be divided into five stages: (i) proto-diastole, (ii) isometric relaxation of the ventricle, (iii) the stage of rapid inflow, (iv) diastasis, and (v) auricular systole. The stage of isometric relaxation of the ventricle begins with the closure of the aortic and ends with the opening of the mitral valve. Clinically its commencement is marked by the second, and its termination by the third heart-sound. In Fig. 1, I have represented, in a purely diagrammatic fashion, the pressure changes which take place in the auricle and the ventricle during the last three stages of diastole. When the mitral valve first opens the pressure in the auricle is considerably higher than that in the ventricle, and during early-diastole blood is rushing rapidly through the mitral orifice. The pressure in the auricle is falling, and that in the ventricle is rising.[3] As soon as the pressure on the two sides of the mitral orifice has been approximately equalized, the rate of blood-flow from auricle to ventricle is greatly reduced, and during diastasis the pressure in both chambers rises slowly as blood flows in from the great veins. When the auricle contracts, the rate of blood-flow through the mitral orifice is again increased, provided that the ventricle is not already full. It is important to note that when the heart is beating slowly, ventricular filling occurs chiefly during early diastole.

(d) *Tachycardia.* In all cases in my series the heart-rate was increased. It was generally between 100 and 120 per minute. Gallavardin (5) has called attention to the same fact.

When the heart is beating rapidly the dynamics of ventricular diastole no longer conform to the description given above. This can be seen from the three records in Fig. 4 which were made on myself after an inhalation of amyl nitrite. The upper tracing in each record is an electrocardiogram, the lower one a pulse tracing. In the first record the heart was beating at the rate of 130 per minute. In the second record, taken thirty seconds later, the heart-rate had slowed down to 110, and in the third record taken four minutes later, it had returned to normal and was 73. In the corresponding diagrams I have represented by black rectangles auricular and ventricular systole as measured from the electrocardiograms. When the heart-rate is

---

[3] See note on page 163, Fig. 1.

73, the auricular complex (P) of the electrocardiogram is separated from the ventricular complex (RST) of the preceding cycle by a time interval of more than three-tenths second, whereas, when the rate is 110 the interval is reduced to about one-tenth second, and when the rate is 130 there is no interval at all, auricular systole following immediately on ventricular systole. In other words, at a heart-rate of 130, the entire diastolic portion of the cardiac cycle is occupied by auricular systole. Even in the second record, when the heart-rate has fallen to 110 per minute, auricular systole must have occurred very soon after the mitral valve opened, for the T-P interval is only one-tenth sec., and most of this period will have been occupied by isometric relaxation of the ventricle.

At all rates of beating, therefore, down to about 90 per minute the phase of diastasis will be eliminated and auricular systole will to a greater or lesser extent overlap the phase of rapid inflow.

Now what is the significance of this overlapping? It means that the rate of blood-flow from auricle to ventricle, which normally is most rapid during early diastole, is still further accelerated by the contraction of the auricle. This abnormally sudden ejection of blood from the auricle into the empty ventricle might, under certain circumstances to be considered below, produce a diastolic ventricular impulse such as occurs in gallop.

(e) *The physiological third heart-sound.* In this connexion one may compare the mechanism of production of the gallop sound with that of the physiological third heart-sound. The third heart-sound was exhaustively studied by Thayer (11 and 12), who, in a consecutive series of 231 healthy persons under the age of 40, found it to be present in 65 per cent. He showed that this sound could be brought out by various procedures which increased the rate of venous return to the heart, such as exercise or elevation of the limbs while the subject lay on his back. He also demonstrated in dogs, a similar sound which corresponded in time to the sudden distension of the ventricle which occurs early in diastole.

The high percentage of cases in which Thayer detected the third heart-sound is doubtless explained by the fact that he was intently searching for it, and that he had adopted the special procedures mentioned above to bring it out. In my own experience, in the course of routine clinical examinations, the third heart-sound is much less frequently noted than Thayer's observations would suggest.

The third heart-sound occurs in early diastole, and its commencement is synchronous, as was shown by Thayer's experiments, with the opening of the mitral and tricuspid valves. It is probably produced by the valve cusps being set into vibration by the blood, rushing under high pressure, through the mitral and tricuspid orifices into the ventricles. When the blood can pass easily from auricle to ventricle, no sound is produced; but when, owing to an increased rate of venous return to the heart, the velocity of the blood-flow is increased, or when the mitral orifice is constricted, as in mitral stenosis, a relative or an actual obstruction is present. This favours the

production of eddies in the ventricle which set the flaps of the mitral valve into vibration and so produce sound. In mitral stenosis, accentuation of the third heart-sound is the usual finding. The third heart-sound and the gallop sound are both due to vibrations set up by an abnormally rapid rate of blood-flow through the mitral orifice, but the cause of the increased rate of blood-flow is different in the two cases. In the case of the gallop sound it is due to contraction of the auricle, whereas in the case of the physiological third heart-sound it is due to a high venous pressure in the auricle at the time when the mitral valve opens. Since the mitral valve opens about one-tenth second after the closure of the aortic valve, the third heart-sound bears a constant relation to the preceding second sound (Fig. 5). The gallop sound, on the other hand, occurs later, for it is related, not to the opening of the mitral valve, but to auricular systole.

Although mitral stenosis is the condition *par excellence* for the development of the third heart-sound, I have never met with true gallop rhythm in a patient who had this lesion. The reason for this appears to be that gallop rhythm occurs only when heart failure is present or imminent. One would not, therefore, expect to find it when the degree of stenosis is trivial. Heart failure in patients with mitral stenosis is almost always the result of auricular fibrillation. This complication rules out the possibility of gallop rhythm, but even in those very rare cases of extreme stenosis, with congestive heart failure and normal rhythm, the conditions are such as to prevent the development of gallop. As I have previously pointed out, an abnormally rapid rate of filling of the ventricle appears to be an essential feature in the production of gallop. Extreme stenosis of the mitral orifice makes rapid filling of the ventricle impossible.

Accentuation of the physiological third heart-sound gives rise to the type of triple rhythm commonly known as ' proto-diastolic gallop'. Proto-diastolic and presystolic (or as I prefer to call it—true gallop) are both the result of an increased rate of blood-flow through the mitral orifice, but whereas in the former this is a purely passive phenomenon and attributable to an increased rate of venous return to the heart, in the latter it is an active manifestation produced by contraction of the auricle.

(f) *Heart failure.* That the increased rate of ventricular filling is not the sole factor in the production of gallop rhythm is obvious; for if it were so, all patients with tachycardia would exhibit gallop.

The other essential factor appears to be the presence of heart failure. The failure may be either of the congestive or of the ischaemic type. It is difficult to make any experimental observations bearing on the significance of heart failure in these cases, but the clinical evidence suggests that the different behaviour of the healthy and the failing ventricle depends on the fact that, whereas the former is able rapidly to accommodate itself to sudden changes in the volume of its contents, the muscle of the ventricle which is lacking in tone is unable to do so. Sudden distension of the ventricle produced by an abnormally rapid rate of filling will then give rise to a palpable

diastolic impulse, and will set the flabby ventricular walls into vibration with the production of sound. The low pitch of the gallop sound suggests that the vibrating structure by which it is produced is the muscular wall of the ventricle and not the valve segments.

IV. *Conclusions*

1. Presystolic gallop is a sign of great clinical significance, and, for this reason alone, it should be clearly distinguished from all other types of triple rhythm.

2. Gallop occurs most frequently in patients with hypertension, advanced coronary disease, or acute inflammatory lesions of the heart.

3. It is an extremely grave sign in prognosis. Very few patients live for more than two years after gallop develops.

4. True gallop rhythm is not causally related to A-V block nor to bundle branch-block.

5. Auricular contraction, tachycardia, and a failing heart are the factors essential to the production of gallop.

6. It is suggested that the additional impulse in gallop is produced by sudden distension of the ventricle, and the additional sound by vibrations of the ventricular wall, both these phenomena being due to an abnormally rapid rate of filling of the ventricle when the myocardium is lacking in tone.

REFERENCES

1. Bramwell, C., *Quart. Journ. Med.*, Oxford, 1935, iv. 139.
2. Bramwell, C., and Hickson, S. K., *Heart*, Lond., 1926, xiii. 133.
3. Campbell, M., and Suzman, S. S., *Lancet*, Lond., 1932, i. 985.
4. Charcelay, *Arch. gén. de Méd.*, 1838, iii. 393.
5. Gallavardin, L., *Arch. des maladies du cœur*, 1920, xiii. 410.
6. Katz, L. N., *Amer. Journ. Physiol.*, 1925, lxxii. 655.
7. Lewis, T., *Quart. Journ. Med.*, Oxford, 1912–13, vi. 447.
8. Lewis, T., *Lectures on the Heart*, N. York, 1915, 61.
9. Mond, H., and Oppenheimer, E. T., *Arch. Int. Med.*, 1929, xliii. 166.
10. Potain, M., *Bull. et mém. Soc. méd. hôp. de Paris*, 1866, iii. 2nd Ser. 138.
11. Thayer, W. S., *Trans. Assoc. Amer. Phys.*, 1908, xxiii. 326.
12. Thayer, W. S., *ibid.*, 1909, xxiv. 71.
13. Wolferth, C. C., and Margolies, A., *Amer. Heart Journ.*, 1933, viii. 441.

DESCRIPTION OF PLATES

FIG. 1.   Diagram of pressure changes in the auricle and ventricle respectively during the three last phases of diastole.   3 = phase of rapid inflow.   I have here represented the pressure in the ventricle as rising.   This may not be correct; for experiments on animals suggest that, although the ventricular volume increases rapidly during this phase of diastole, there may be no appreciable increase in intra-ventricular pressure. 4 = diastasis.   5 = auricular systole.

FIG. 2.   Record from a patient exhibiting bundle branch-block and gallop rhythm. (a) electrocardiogram leads I. II. III.   (b) electrocardiogram lead II (unstandardized) and phonocardiogram recorded with Western Electric Company's electrical stethoscope and string galvanometer.   The first heart-sound in each cycle consists of two series of vibrations which are very similar in form.   The second series of vibrations commences during the S wave of the electrocardiogram : the first series follows the P wave.

FIG. 3.   Electrocardiogram (unstandardized) and phonocardiogram from a patient with gallop rhythm.   The phonocardiogram is recorded with Matthews' oscillograph and condenser microphone.   It illustrates the time relations of the 1st (1), 2nd (2) and gallop (G) sounds to the R, T, and P waves of the electrocardiogram.   The lower record was taken from the same patient with the oscillograph made rather more sensitive.

FIG. 4.   Electrocardiograms and optical carotid pulse tracings taken during recovery from an inhalation of amyl nitrite, to illustrate the curtailment of diastole during the tachycardia.   (a) 80 seconds after commencement of inhalation.   Heart-rate 130. T-P interval 0.   (b) 110 seconds after commencement of inhalation.   Heart-rate 100. T-P interval 0·1 second.   (c) 360 seconds after commencement of inhalation.   Heart-rate 73. T-P interval 0·3 second.

FIG. 5.   Electrocardiogram and phonocardiogram recorded with a Matthews' oscillograph and condenser microphone, from a patient with advanced mitral stenosis. (1) first heart-sound, (S.M.) systolic murmur, (2) second heart-sound, (3) third heart-sound, (D.M.) diastolic murmur.

FIG. 1

FIG. 2

Fig. 3

FIG. 4

FIG. 5
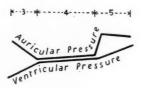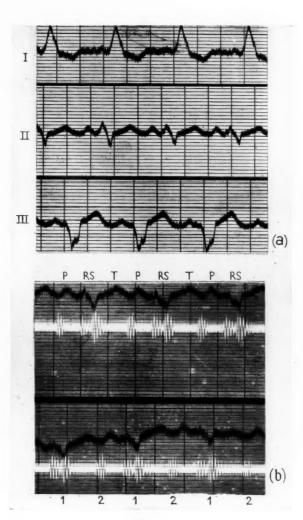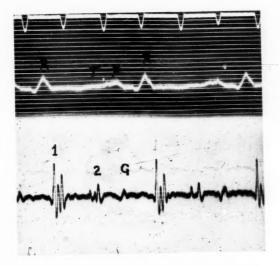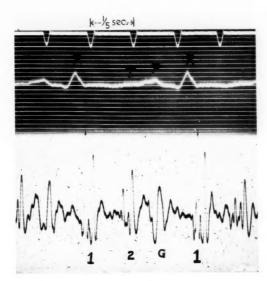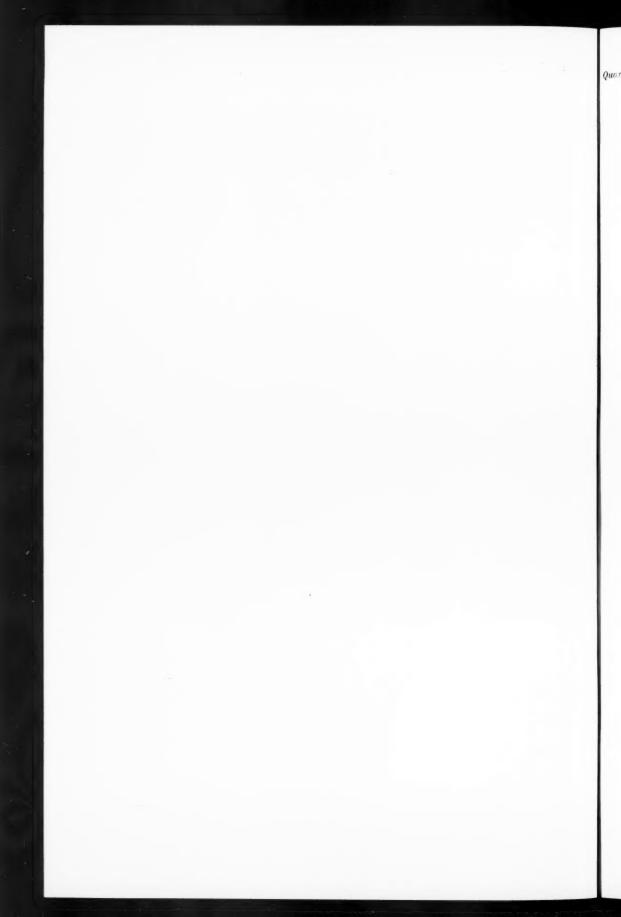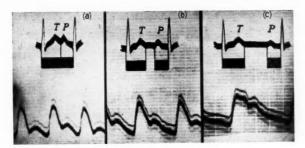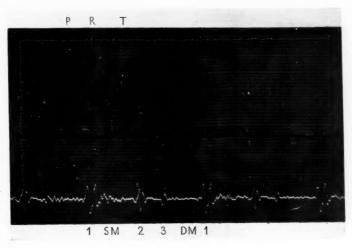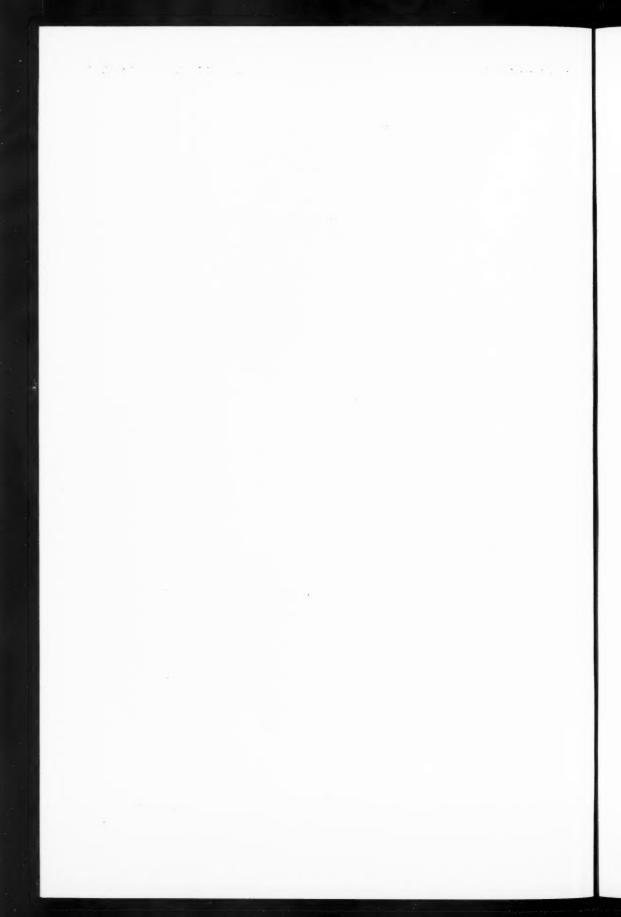
616.151.5

HEREDITARY PSEUDO-HAEMOPHILIA [1]

By R. S. HANDLEY, and A. M. NUSSBRECHER
(From the Middlesex Hospital)

FROM time to time there are published in the medical journals cases of the haemorrhagic diathesis, usually with a familial or hereditary history, which do not fit into any accepted classification. Frank first proposed the term pseudo-haemophilia for such cases ; and in 1926 von Willebrand (17) separated from this indefinite group a form of bleeding which was inherited as a dominant sex-linked character, and reserved the name Hereditary Pseudo-haemophilia for this type alone. An account is given below of a family resembling that described by von Willebrand and, although it is not established that this family is identical with von Willebrand's in all respects, yet the likeness is sufficiently marked to justify a provisional diagnosis of hereditary pseudo-haemophilia.

In haemophilia proper the bleeding tendency is a recessive sex-linked character, appearing only in males, and being transmitted characteristically through the female. The mode of inheritance, as enunciated by Lossen and Nasse, is well known and can be best explained diagrammatically by taking according to convention X and Y as the chromosomes which determine sex, and x as the chromosome which carries the recessive sex-linked character. Thus where XX is the normal female and XY the normal male, there are two likely combinations, and three further possible ones (Fig. 1).

In pseudo-haemophilia the bleeding tendency is a dominant sex-linked character, and an affected mother or father may beget children of either sex who will show the tendency to bleeding. The five combinations shown in Fig. 1 hold equally true for pseudo-haemophilia, if x be regarded as carrying the dominant bleeding tendency,[2] and it will be seen that two types of female bleeder are possible, the mild xX and the severe xx ; whereas there can only be one type of pseudo-haemophilic male, xY. This will be further discussed when considering von Willebrand's family.
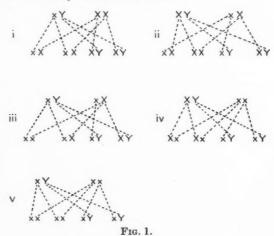
The first record of the family which we have investigated was published in 1886. In that year Treves (13) described a girl with haemophilic symptoms who came under his care, and he gave a family tree which showed that the girl's parents were first cousins and descendants of a haemophilic man. In

[1] Received November 5, 1934.

[2] It is conventional to designate a dominant character by the capital letter and the recessive by the small letter. In this paper small x is used for the chromosome carrying the bleeding tendency whether dominant or recessive.

1911 the family was re-examined by Bulloch and Fildes (3), who published a long note on its history in their monograph on haemophilia. They conclude by doubting whether there is adequate evidence of haemophilia, and their doubts appear to have arisen largely because they were unable to accept the idea of haemophilia occurring in women. Recently this family has again presented itself at the Middlesex Hospital through the son of one of the bleeder women whom Bulloch and Fildes examined, and the evidence of haemophilia seemed to be so strong in this particular lad that a further investigation of the family was undertaken.

Fig. 1.

A scrutiny of the family tree (reproduced from Bulloch and Fildes, pedigree 493, and brought up to date) shows that, even in its early stages, it does not behave as true haemophilia; for, prior to the first cousin marriage in the fourth generation, the bleeding tendency was handed down directly from father to son in three families. This is too frequent an occurrence to be accounted for by the accidental marriage of a haemophilic man to a ' carrier ' haemophilic woman. In all, six sons inherited the bleeding tendency from their three respective fathers, namely II 3 and II 4 from I 3, III 1, III 3, and III 5 from II 3, and IV 7 from III 1. It is true that the tree shows three instances in which inheritance of bleeding behaves according to Nasse's law, for II 3 transmitted the taint through his apparently healthy daughters III 9 and III 13 to his grandsons IV 14 and IV 26, and IV 14 to his grandsons VI 5, 6, 7, 8 through V 8, but these account for only six of the twenty bleeders in the pedigree.

We now come to the first-cousin marriage in the fourth generation. Until then, no female bleeder had been recorded. In considering this marriage it is known that the husband was a bleeder. The wife presents the problem as to whether she was a haemophilic carrier or a mild pseudo-haemophilic. Her brother and sisters did not survive infancy, and no evidence is therefore available from them. She herself strenuously denies that she has ever

suffered from any form of bleeding whatsoever; yet the fact remains that of her ten children, two were bleeder males, four were bleeder females, and one was a carrier female. Such a family is incompatible with a normal mother (Fig. 1). It does not quite fit in with a pseudo-haemophilic mother since then all the daughters should have bled, half severely and half mildly (Fig. 1, iii), and it is only possible to conclude that the mother and half of
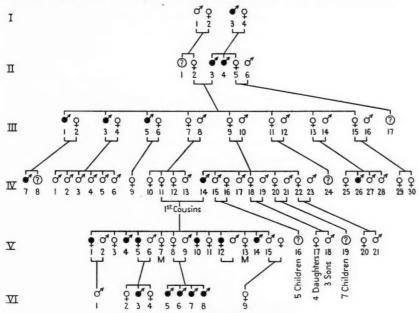
FIG. 2. *Tree of Family Recorded.*

1. The tree is labelled to correspond with Bulloch and Fildes' tree.
2. Several members, particularly in the sixth generation have been added.
3. Not all those recorded by Bulloch and Fildes as bleeders are recorded as such here.
4. M = miscarriage.

her daughters were pseudo-haemophilics of the mild xX type if one agrees with von Willebrand's somewhat weak explanation that the bleeding tendency may be so slight as to pass unrecognized. Nor are the facts compatible with a 'carrier' haemophilic mother, unless one is prepared to accept the existence of homozygous haemophilic women showing the classical symptoms of the disease. It might even be supposed that this was a case where bleeding was inherited as a simple dominant. The first-cousin marriage and its results would then be represented symbolically as follows (where R = recessive, D = dominant character): RR♀ multiplied by DR♂ = 2DR + 2RR, i.e. equal numbers of bleeder and healthy children. At first sight this accords exactly with the facts, but it is invalidated by the progeny of one of the healthy daughters (V 8) consisting of four bleeder sons (VI 5, 6, 7, 8).

A further point in connexion with this first-cousin marriage must be considered. By certain authorities, notably Gates (6) quoting Schloesman in

support, it is held that the carrier females in haemophilic families may show an abnormal tendency to bleed, and the fact that the daughters of the marriage showed bleeding symptoms would not militate against a diagnosis of true haemophilia.   The mass of evidence is against the occurrence of bleeding in heterozygous women, at any rate, for Bulloch and Fildes (3) in 1911, after studying over 900 cases, concluded that ' no case (of haemophilia) has yet been described in a female which bears more than a superficial resemblance to the disease as found in the male ', and ' all statements alleging the occurrence of well marked haemophilia in females are unsupported by adequate evidence '.   They divide haemophilia occurring in women, as described in the literature, into three types :

(1) Well-marked haemophilia, implying symptoms in females comparable to those occurring in males. They could find no case supported by evidence, and their remarks quoted above refer to this class.

(2) An abnormal tendency in females to bleed, without there being any obvious connexion between such females and bleeder families.   This class they dismiss as irrelevant.

(3) An abnormal tendency to bleed in female members of admitted haemophilic stock, such tendency being slight or atypical compared with ' well-marked haemophilia '.   Of this class they collected nineteen cases, but in every instance found the evidence very weak.   Recently Foulis and Crawford (5) have recorded a case which seems to fall into this class, but unfortunately they were unable to carry out full investigations.

The combination of circumstances required to produce a homozygous haemophilic woman (Fig. 1, iii and v) appears only to have arisen twice in the literature of the disease.   Careful survey of the pedigrees in Bulloch and Fildes' work reveals thirteen marriages between cousins, and in two instances the husband was a bleeder while the wife proved herself a carrier by bearing a bleeder son.   The first case occurred in the famous Mampel family (pedigree 389 in Bulloch and Fildes) and the children of the marriage consisted of six healthy daughters and one bleeder son.   The second case occurred in a family recorded by Wightman (16) in 1894 (pedigree 431 in Bulloch and Fildes) in which the marriage produced three healthy daughters and a bleeder son, but the history is so scanty that it cannot be said to be of much value.   Bauer and Wehefritz (1) have stressed the fact that the case in the Mampel family is a biological experiment of great importance, and they consider that the healthy female progeny must indicate that the homozygous condition is so lethal as to preclude the development of the fertilized ovum.   For this reason no homozygous female is ever born. The evidence on this point, however, consisting as it does of one or possibly two families, is not sufficiently ample to justify a dogmatic statement, but this speculation is a fascinating one.

The following are the histories of the three cases which we have investigated personally, in the order in which they have come under notice.   An appendix records the histories of the rest of this family.

VI 3, Albert H. (Middlesex Hospital Reg. No. 54921); twenty-one years old in 1934. Ever since he can remember he has bruised easily. During the War he was hit on the head by a piece of falling shrapnel and the injury was accompanied by violent headache and severe epistaxis. He has always been prone to epistaxis, which was so severe when he had whooping cough at the age of eight that he lost consciousness, and his life was despaired of. Cuts have always bled excessively, one on the thumb in 1933 not ceasing to bleed for a month. He has suffered severely from haemarthrosis, particularly in the left knee. This joint was injured eight years ago at football, since when it has swollen and subsided many times, the swelling lasting from a few days to many months. On one occasion the knee was aspirated by a doctor, blood being withdrawn, but the swelling rapidly reaccumulated. The swelling is accompanied by pain and stiffness, and other joints, notably the ankles, have been affected to a slighter degree.

It was on account of his left knee that he was admitted to the Middlesex Hospital in February 1934, under the care of Dr. T. Izod Bennett. He was a pale but well-built young man, with the cheerful care-free disposition said to be the characteristic of the bleeder. On examination the knee was tender and greatly swollen and presented the features of an effusion into the joint. The thigh and calf muscles of the affected limb showed some wasting. X-ray showed rarefaction of the bones forming the joint, with roughening of the articular surfaces of tibia and patella, though there was no calcification of the blood-clot. The general clinical examination showed nothing except some bad teeth. The spleen was impalpable. A blood count showed that haemoglobin was 105 per cent., red cells 5,700,000, colour index 0·9, fragility of red cells normal, white cells 10,000, neutrophils 65 per cent., lymphocytes 26 per cent., monocytes 7 per cent., eosinophils 2 per cent., and blood-platelets 300,000. The clotting time (all clotting times are by the Lee and White method with two exceptions which are specified) estimated weekly for two months, showed times of 7, $10\frac{1}{2}$, 10, $10\frac{1}{2}$, 11, $5\frac{1}{2}$, 5, and 13 minutes, as against an average control time of 5 minutes. The Wassermann reaction was negative. The blood calcium was 10 mg. per cent.

The patient was treated while in hospital with hen serum after the method described by Vines, but, though this appeared to cause slight improvement in the clotting time, its effects were fleeting. He was discharged with a walking caliper to rest the knee.

Since discharge he has visited the hospital at intervals and has shown bruises with no antecedent history of injury, one in particular being the size of a saucer and situated on his thigh. Six months after the discharge the platelets were 200,000 per c.mm., bleeding time five and a half minutes (control five minutes) and coagulation time twelve minutes (control five and a half minutes). At the examination the patient complained of recent epistaxis and stiffness of one interphalangeal joint of the ring finger which was swollen.

V 5, Minnie H. (Middlesex Hospital Reg. No. 31006), mother of the above patient, was seen by Bulloch and Fildes (3) in 1910, and was described as a somewhat poorly developed young woman of twenty-six, with many decayed teeth. They note that she was alleged to be a great sufferer from epistaxis. At seventeen she had received a deep cut on the head from a falling bottle, for which she had been treated for some weeks, first at Greenwich Hospital, and then, as great swelling ensued, at the London Hospital. She began to menstruate at the age of eighteen, but only after marriage at twenty-five

did she lose unusual quantities of blood at the periods. At twenty she cut her hand on a broken bottle and the wound bled for five weeks.

Personal questioning of her has elicited the following points. Her age is now fifty years. Her joints have frequently swelled—knees, ankles, elbows, and wrists, and occasionally one hip being affected. The swelling lasts from a few days to a few weeks, and there may be no antecedent trauma. Recently her knee has been swollen for three weeks. She bruises at the slightest knock. She had eight teeth extracted at the London Hospital, and the sockets subsequently bled for weeks. One tooth was extracted at the Middlesex Hospital in 1932, and the bleeding which followed lasted for a month. Cuts on the fingers may bleed for weeks, and she has had haematuria. The periods have been profuse, and at times she has not ceased bleeding for months on end. There have been three confinements, after all of which she has been compelled to stay in bed for four months, on account of bleeding.

While in this hospital in 1932 she gave a history of haematuria of ten weeks' duration earlier in the year, with bilateral lumbar pain : for this she had been fully investigated at St. Paul's Hospital with negative results. During her stay at the Middlesex, blood counts showed the following condition :—

Date.	5.5.32.	31.8.32.	26.9.32	21.10.32.
Coagulation time	22 min.	7½ min.	12 min.	11 min.
	(Wright)	(Lee and White)	(Lee and White)	(Lee and White)
Control time	15 min.	3 min.	3–4 min.	3 min.
Platelets	275,000	—	184,000	—
Haemoglobin	80 %	75 %	—	78 %
Red cells	4,130,000	3,600,000	4,890,000	3,740,000
White cells	6,400	—	—	5,000
Polymorphs	64 %	—	—	55 %
Lymphocytes	30 %	—	—	38 %
Monuclears	6 %	—	—	3 %
Bleeding time	—	—	5½ min.	5 min.

In June 1934 she was admitted to this hospital for menorrhagia of six months' duration under the care of Mr. F. Roques, who thought that this must be due to fibroids. She did not respond to radium treatment, and was transferred to a medical ward under the care of Dr. Lakin, for treatment of her anaemia.

On 2.7.34 the haemoglobin was 62 per cent. and red cells 3,240,000. On 12.7.34 the haemoglobin had risen to 70 per cent. and the red-cell count to 4,030,000. Five readings of her clotting time averaged eight minutes, and Vines's hen serum treatment had no effect. Clinical examination revealed nothing abnormal except bad teeth. The spleen was not palpable. The Wassermann reaction negative.

Although her clinical condition improved, bleeding from the vagina continued up to the time of her discharge, and persisted for another eight weeks. A recent examination showed 5,140,000 red cells per c.mm., 100 per cent. haemoglobin and 220,000 platelets per c.mm. The coagulation time by Wright's method was forty-six minutes (control ten minutes) and bleeding time was normal. Her blood calcium was 11·4 mg. per cent.

V 12, Ada B., forty-three years old in 1934 (Middlesex Hospital Reg. No. 61340), is the sister of the above patient. She bruises readily and has always bled easily from small cuts, often for three or four days. At the age of ten in particular she bled excessively from a cut lip. She has had periodic haematuria, one attack at the age of eighteen necessitating in-patient treat-

ment at the London Hospital for a fortnight. Her periods last from ten days to a fortnight and have always been copious. She has been married for five years and had a miscarriage three years ago. On this occasion she lost blood for about twenty days subsequently. A second miscarriage eighteen months ago, occasioned her removal to hospital as she bled for six weeks; but a polypus was found, and this was considered sufficient to account for the bleeding. Two years ago at King's College Hospital she had a tooth extracted and bled for a fortnight. She has had occasional swelling and stiffness of her joints—knees, ankles, and elbows being affected.

Clinical examination on 13.6.34 showed nothing abnormal except bad teeth, and some bruises on the right arm. The spleen was not palpable. Examination of the blood gave a red count of 5,500,000, platelet count of 265,000, and a bleeding time within normal limits. The coagulation time was fourteen minutes (control five and a half minutes). The Wassermann reaction was negative, and it is interesting to note that the blood taken for this purpose which was not shaken regularly did not clot for many hours.

Discussion

The literature on pseudo-haemophilia is not nearly so extensive as that on haemophilia; in fact von Willebrand appears to be the only writer on the condition in its specific sense. He made a preliminary communication in 1926 (17) and subsequently expanded his theme (18). The family investigated lived in the Åland Islands in the Baltic. There were 58 members, 23 of whom were bleeders, 16 out of the 32 women and 7 of the 26 men being affected. He found that the diathesis shows itself in women in a slight and severe form, whereas in men there was only one form. He showed the tree, which is reproduced, to Prof. Federley, Professor of Genetics at Helsingfors, who was of opinion that the family showed inheritance of a dominant sex-linked character, residing in the X chromosome; and, because in the male there is only one X chromosome, a man can only show the disease in simple form, whereas in the female two types are seen, depending on whether the female is homozygous or heterozygous for the X chromosome. The author points out that family J of his tree gives an almost ideal theoretical result, whereas in family S, in which half the women should in expectation be heterozygous, this is not the case. He explains this on the assumption that the bleeding tendency may be latent.

The main clinical symptom of his cases was their tendency to bleed. The clinical examination was on the whole negative, though some showed a secondary anaemia and some were weakly and ill. Nearly all the affected people suffered from epistaxis, and bleeding from the gums was common, as was bleeding from the female genitalia. Bleeding also occurred from stomach, intestines, and urinary tract, but only one instance of haemarthrosis is recorded. No splenic enlargement was ever found. There were six fatal cases of haemorrhage, all in women, one of post-partum haemorrhage, one of bleeding from the nose, mouth, gut, and genitalia, two of intestinal bleeding, one of bleeding from an injury to the tongue, and one of bleeding from the stomach.

Von Willebrand thinks that bleeding may commence at birth, or remain latent for several years. With advancing age the tendency may remain, decrease, or disappear.

The haematological findings, in addition to the changes of secondary anaemia, showed a normal white-cell count, and the few platelet estimations performed were normal. One isolated observation showed rapid clot retraction.

Von Willebrand has summarized his ideas on the differential diagnosis between true and pseudo-haemophilia in the following table:

	Haemophilia.	*Pseudo-haemophilia.*
Inheritance	Sex-linked recessive	Sex-linked dominant
Sex	Men	Both
Platelet count	Normal	Normal
Bleeding time (Dukes)	Normal	Increased
Coagulation time	Increased	Normal
Rumpel Leede test [3]	Negative	Positive
Needle-prick test [3] (Koch)	Negative	Positive

♂, ♀ = Mild Bleeder. D = Dead From Bleeding.
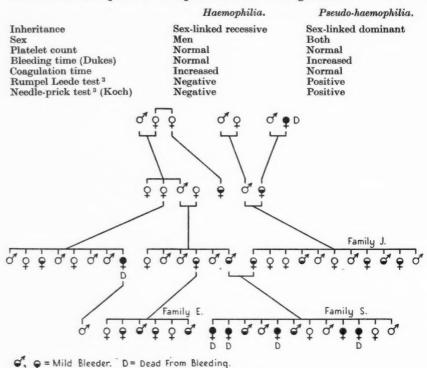
FIG. 3. *Von Willebrand's Tree.*
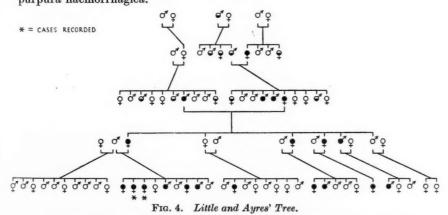
It is perhaps unfortunate that von Willebrand and Jurgens (19, 20) have since twice re-described the family under the term constitutional thrombopathy (Konstitutionelle Thrombopathie). These last papers discuss some

[3] With regard to the two latter tests, it has been impossible to discover what the Koch needle-prick test is. The Rumpel Leede test appears to be identical with Hess' capillary resistance test. As the significance of this test was not realized till after our patients had left hospital, it is only possible to give the results of a single test on four individuals. Of the cases considered in detail, Albert H. (VI 3) gave a negative result, and Minnie H. (V 5) gave a strongly positive result. Of the cases recorded in the appendix, George P. (IV 14) gave a negative result, and Lily H. (V 10) gave a very faintly positive result.

work on the platelets of the cases where, by use of the capillary thrombo-meter devised by Morawitz and Jürgens (12), it was found that the platelets showed delayed clumping time.   The platelets were also of irregular size, some being macro-, others micro-platelets.   As far as can be discovered the thrombometer has not been used on the blood of undoubted haemophilics ; and the papers seem to add a speculative synonym to an already confused nomenclature.

Buckman (2) records two interesting cases (Cases I and II) who were brother and sister.   The girl was admitted to hospital on the first occasion for profound anaemia from a wound of the lip, and on the second occasion for bleeding from a wound of the hard palate and multiple ecchymoses on the body.   On both occasions she was repeatedly transfused.   She had pro-longed bleeding and coagulation times, though the platelets were normal. Her brother was admitted to hospital with epistaxis and skin ecchymoses. He had a prolonged bleeding time with slightly prolonged coagulation time and normal platelet count, and subsequently died.   Of the relations, the paternal great grandfather, grandfather, father, four paternal uncles, and one paternal aunt also bled unduly from wounds.

Hess (8) considers that in haemophilia the male members of an affected family show classical symptoms, but the females may suffer from a purpuric type of bleeding.   He thinks that on account of the family history hereditary purpura is often mistaken for haemophilia.   Most of the cases of his paper have lowered platelet counts and appear to resemble a hereditary form of purpura haemorrhagica.

FIG. 4.   *Little and Ayres' Tree.*

Little and Ayres (9) have published the family tree of two sisters who suffered from profuse bleeding, one developing a haemarthrosis.   The tree and clinical findings are similar to von Willebrand's family, except that the spleens in both cases were enlarged.   Splenectomy was performed for one patient, as a last resort, and death occurred a few hours after operation. The spleen thus removed showed no microscopic or macroscopic abnormality apart from enlargement.

Minot (11) describes a case of hereditary bleeding handed directly from father to son for five generations. Epistaxis and multiple ecchymoses, in the absence of lowered platelet count or increased coagulation time, were the chief symptoms. Bleeding time was prolonged. One woman was affected. The disease was of a mild type, for no grave haemorrhage is mentioned.

Giffen (7) records a number of cases of mysterious haemorrhage, and his Case III is of special interest. The patient, a woman of thirty-three, suffered from excessive bleeding from trivial injuries, from epistaxis, and from menorrhagia. Her clotting time and platelet count were normal, but the bleeding time was prolonged. The presence of a duodenal ulcer renders the occurrence of gastro-intestinal haemorrhage irrelevant. Her maternal great-grandmother, grandmother, and mother also suffered from undue bleeding.

Warde (15) observed a woman who came under her care for carcinoma of the breast. The family history was one of undoubted haemophilia. At the age of ten Warde's patient bled to such an extent from a socket after tooth extraction that she became unconscious. Later she was treated at hospital for haemorrhage from a cut thumb. At twenty-one an abscess in the mouth was incised, and bleeding continued for fourteen days, necessitating her retiring to bed. At the birth of her only child, a boy, she had a post-partum haemorrhage. The infant subsequently died of a rectal haemorrhage. This woman was the only female bleeder in a family which otherwise behaved strictly according to Nasse's law. Warde considers that she belongs to class III of Bulloch and Fildes's classification of female haemophilics. No unusual haematological findings are recorded at the time that Warde investigated her, but this is not surprising in view of the fact that a radical mastectomy was followed by nothing more alarming than prolonged oozing of bloodstained fluid.

Curious cases of familial haemorrhage are recorded by Austin and Pepper (21), Curschman (22), Glanzman (23), Kehrer (24), Krömeke (25), Lloyd (26), Rosling (27), and Rothman and Nixon (28). Their papers are worth consulting.

A search of the available literature since 1911 has revealed nothing further of interest, except single instances of inexplicable haemorrhage, frequently of gynaecological origin. The futility of recording such cases under the name of haemophilia, often in the absence of family history, platelet count, and even coagulation time, is obvious.

As regards the treatment of pseudo-haemophilia our results are of little value as they are based on two cases only. There appeared to be some slight benefit in one case from Vines's serum treatment (14). It is clear, however, that treatment must proceed on the same lines as used in haemophilia. In the latter disease transfusion is still the most effective method of stopping haemorrhage. Serum treatment seems to hold out considerable hope, but Birch's method of injecting theelin has been largely abandoned. The matter is summarized in a paper by Mills (10).

Discussion of the mechanism of bleeding in pseudo-haemophilia would appear to be useless so long as the major problems of the coagulation of normal blood remain matters of controversy among physiologists.   Von Willebrand and Jürgen's work (19, 20) points to some abnormality of the platelets being the most likely cause of the prolonged bleeding, but more evidence must accumulate before this hypothesis can be proved or disproved.

The diagnosis of pseudo-haemophilia must rest on an adequate family history and unequivocal symptoms of bleeding, supported by very complete blood investigations.   Von Willebrand (18) states that in pseudo-haemophilia clotting time is normal and bleeding time prolonged.   The very reverse is true of the cases here recorded, and our findings tally with those of true haemophilia.   But these two investigations are subject to many pitfalls, and too much reliance cannot be placed upon isolated readings.   The clotting time varies in the same individual from time to time ; and the bleeding time, owing to the lack of standardized technique, at present needs considerable experience in the interpretation of results.

To conclude, it must be emphasized that two possibilities have to be weighed in considering this family.   It may be an example of pseudo-haemophilia, or it may be an example of haemophilia with the production of the first homozygous females recorded.   We have clung rather to the former view owing to the evidence of the Mampel tree and Wightman's family, together with the direct transmission of bleeding seen in the earlier part of our tree.   Those who would support the latter view must be prepared to accept the occurrence of bleeding in homozygous females.

Summary

1. A family is described in which the classical symptoms of haemophilia appear in women.

2. Following von Willebrand's original paper, the term pseudo-haemophila is used to describe the condition.

3. The possibility that the female bleeders are the first homozygous haemophilic women to be recorded cannot be excluded.

4. The literature on hereditary bleeding in women is very briefly considered.

The following notes give the histories of the bleeder members of the tree. One or two sentences only are devoted to the healthy members, for their history is clearly one of absent symptoms. The histories have been compiled from Treves's original paper, from Bulloch and Fildes's work, and from our own questioning of eight different members of the family.

I 3, George B.   There are no details furnished of this man except the tradition that he was a bleeder and that he lived to the age of ninety-nine, being bedridden for the last twenty years of his life.

II 3 and II 4.   Again only tradition asserts that these men were bleeders.

III 3, Stephen B.   The eldest of his family (not, as Bulloch and Fildes state, the second son) suffered from excessive bleeding from cuts.   He lived to old age.

III 1, Daniel B, and III 5, Stewart B.   Both suffered from epistaxis and excessive bleeding after cuts.   They lived to old age and were dimly remembered by those whom we interviewed.

IV 1, Frederick B.   Died of haemorrhage from the ankle at Derby, having trapped his ankle in a railway point.   Apparently Bulloch and Fildes's statement that he had both legs crushed by a locomotive is incorrect.   Nothing further of him could be recalled.

IV 7 is said to have been a bleeder, but there is no further history.   He is figured as a bleeder.

IV 14, George P., is still alive and we were able to take his history personally.   Bulloch and Fildes express grave doubts as to whether there is any evidence of haemophilia, but his own story is quite convincing.   He has bled severely from cuts on the hand three times.   A cut on the little finger necessitated twelve visits to the London Hospital before it stopped bleeding. A cut on the thumb exsanguinated him to such a degree that his friends laid him out in the belief that he was dead.   A cut on the ring finger also bled severely.   He has, during his life, had one tooth extracted, and remembers sitting up for several nights after it, spitting blood into a bowl.   He has frequently had bouts of haematuria, but never trouble with his joints.   He bruises easily, and we saw, on the occasion of our visit to him, an ecchymosis raised by catching his hand on one of the hooks of his boot.

IV 15, Joseph P., bled but little externally. He had trouble with his hip, but this was apparently of traumatic origin.   There is in his case no evidence of bleeding and he is recorded in the tree accordingly.   His progeny is healthy.

IV 17, William P., is figured as a bleeder in Bulloch and Fildes's tree, but his brother, IV 14, denies that he ever bled excessively.   He is accordingly figured as healthy.

IV 26 is said to have been a bleeder, but nothing definite could be discovered.   He is figured as a bleeder.

V 1, Florence P., was Treves's patient.   She came to Treves's notice at the age of six on account of bleeding after dental extraction.   It was the first occasion on which a bleeding tendency had been noted in her.   On admission to the London Hospital she was completely blanched and watery blood was issuing from her mouth.   She was discharged fourteen days later.

From that time she suffered from epistaxis, and bruised easily. At fourteen years of age she started to menstruate and the periods were marked by their abundance, but were regular. At about twenty, she struck herself on the lip with a hammer and the wound bled profusely, but the haemorrhage was easily arrested at Greenwich Hospital. She married at twenty-one and became pregnant. A fortnight before labour she had an ante-partum haemorrhage which continued up to parturition and she died three hours after the birth of her child.

V 4, Albert P., was a 'terrible bleeder'. As a baby he bit his tongue and the haemorrhage was severe enough to warrant his admission to the London Hospital. A cut over the eyebrow, sustained when he was eight years old, bled severely even after the insertion of stitches. There was no bleeding during the first dentition. When about sixteen he fell over a pole, injuring his knee, for which he was admitted to Shadwell Hospital. A year later this joint was again injured and he was admitted to the London Hospital under Mr. Warren Tay, the knee being much swollen and discoloured : he was in hospital for seven weeks, and soon after discharge was readmitted for a week for the application of a gum and chalk splint. He bled excessively from minor cuts and from carious teeth. He died a few years later of haemoptysis. Bulloch and Fildes say : 'He is not lame and can walk for miles. He is a strong dock labourer, an occupation which does not seem to us compatible with the idea that he is a genuine bleeder'; but close inquiry reveals that he was in casual employment at the docks and worked during intervals of good health.

V 5, Minnie H., is described fully in the body of the paper.

V 8, Edith J., does not bleed badly. She bruises easily, but menstruation has not been excessive. She was admitted to the London Hospital for inevitable abortion, when three months pregnant, there being a history of two days severe haemorrhage. On this occasion the uterus was emptied and a hot douche checked further bleeding. Four subsequent deliveries have been uneventful. She is not figured as a bleeder.

V 10, Lily H., was seen by us. As a small child she bit her tongue and had to receive out-patient treatment at the London Hospital. She was kicked on the knee when fourteen years old and the joint subsequently swelled. She was treated for this at the London Hospital. Subsequently she was in bed for two years in an attempt to get the swelling to subside. She suffers from menorrhagia and intermittent haematuria. She also bleeds excessively from small cuts, and bruises easily. A recent examination of her blood showed : R.B.C. 6.030.000 per c.mm., Hb. 100 per cent., Platelets 300,000 per c.mm., coagulation time (Lee and White) 12 minutes, (normal 4 to 7 minutes), bleeding time within normal limits. She is figured as a bleeder.

V 12, Ada B. Her history is considered in detail in the paper.

V 14, William P., bled severely at the age of five from a cut at the back of his head. He is alleged to have bruised easily, and swellings, sometimes due to knocks, would appear and burst, discharging red fluid. Bulloch and Fildes considered that he was affected in slight degree, with a tendency to the production of haematomata, but that there was no evidence that he was a genuine bleeder. With this it is difficult to agree, for his mother states that he suffered from periodic swelling and stiffness of joints. He played a cornet, and died at the age of twenty-nine of pulmonary haemorrhage after months of haemoptysis. He is figured as a bleeder.

VI 3, Albert H., is our patient and his history is considered in detail elsewhere.

VI 4. Died in infancy from an alleged cerebral haemorrhage. This is not supported by sufficient evidence to permit of her being included as a bleeder.

VI 5, Frank J., bled severely after a dental extraction at the Tilbury Hospital, being 'on the danger list'. His ankles used to get stiff and swollen, but he appears to have outgrown this. He has had haematuria and epistaxis. He is figured as a bleeder.

VI 6, Ernest J. Bleeds from cuts to an excessive degree. His knee has given him much trouble, there being here again the history of periodic swelling and stiffness. As an infant he became dangerously exsanguinated, following haemorrhage after circumcision. He is figured as a bleeder.

VI 7, William J. Bleeds rather easily from cuts and has severe epistaxis. He is figured as a bleeder.

VI 8, Harry J., also suffers from epistaxis and undue bleeding from small cuts. He is figured as a bleeder.

REFERENCES

1. Bauer, K. H., and Wehefritz, E., *Arch. f. Gynaek.*, Berl., 1923–4, cxxi. 462.
2. Buckman, T. E., *Amer. Journ. Med. Sci.*, Philad., 1928, clxxv. 307.
3. Bulloch, W., and Fildes, P., *Eugen. Lab. Memoirs*, Lond., 1911, xii.
4. Cockayne, E. A., *Inherited Abnormalities of the Skin and its Appendages*, Lond., 1933.
5. Foulis, M. A., and Crawford, J. W., *Brit. Med. Journ.*, Lond., 1934, ii. 594.
6. Gates, A. R., *Heredity in Man*, Lond., 1929.
7. Giffen, H. Z., *Amer. Journ. Med. Sci.*, Philad., 1928, cxxv. 44.
8. Hess, A. F., *Arch. Int. Med.*, Chicago, 1916, xvii. 203.
9. Little, W. D., and Ayres, W. W., *Journ. Amer. Med. Assoc.*, Chicago, 1928, xci. 1251.
10. Mills, C. A., *Journ. Lab. and Clin. Med.*, St. Louis, 1931, xvii. 932.
11. Minot, G. R., *Amer. Journ. Med. Sci.*, Philad., 1928, clxxv. 301.
12. Morawitz, P., and Jürgens, R., *Münch. med. Wchnschr.*, 1930, lxxvii. ii. 2001.
13. Treves, F., *Lancet*, Lond., 1886, ii. 533.
14. Vines, H. W., *Quart. Journ. Med.*, Oxford, 1920, xiii. 257.
15. Warde, Mildred, *Brit. Med. Journ.*, Lond., 1923, ii. 599.
16. Wightman, J. P., *Lancet*, Lond., 1894, i. 535.
17. Willebrand, E. A. von, *Finsk. läkaresallsk. Handb.*, Helsingfors, 1926, lxviii. 87.
18. Willebrand, E. A. von, *Acta Med. Scand.*, Stockholm, 1931, lxxvi. 521.
19. Willebrand, E. A. von, and Jürgens, R., *Klin. Wchnschr.*, Berl., 1933, xii. i. 414.
20. Willebrand, E. A. von, and Jürgens, R., *Deutsches Arch. f. klin. Med.*, Berl., 1933, clxxv. 453.
21. Austin, S. H., and Pepper, O. P., *Arch. Int. Med.*, Chicago, 1913, xi. 305.
22. Curschman, H., *Klin. Wchnschr.*, Berl., 1930, ix. i. 677.
23. Glanzman, E., *Jahrb. f. Kinderh.*, Berl., 1918, ii. i.
24. Kehrer, F. A., *Arch. f. Gynaek.*, Berl., 1876, x. 201.
25. Krömeke, F., *Deutsche med. Wchnschr.*, Leipz., 1922, xlviii. ii. 1102.
26. Lloyd, B., *Journ. Hered.*, Wash., 1925, xvi. 28.
27. Rosling, E., *Acta Med. Scand.*, Stockholm, 1929, lxxii. 104.
28. Rothman, P. E., and Nixon, N. K., *Journ. Amer. Med. Assoc.*, Chicago, 1929, xciii. 15.

616.12–008.331.1

AN ATTEMPT TO DEMONSTRATE A PRESSOR SUBSTANCE IN THE BLOOD IN MALIGNANT HYPERTENSION[1]

By R. S. AITKEN and C. WILSON

(From the Medical Unit, the London Hospital)

With Plate 22

ESSENTIAL hypertension and hypertension associated with chronic nephritis have long been recognized as clinically distinct. Volhard has named the former ' red hypertension ' and the latter ' pale hypertension '. ' Pale hypertension ' occurs in two groups of cases: (1) those in which an acute nephritis is succeeded by a chronic nephritis, (2) those in which albuminuria, anaemia, retinitis, renal insufficiency, and other features of a chronic nephritis develop insidiously, sometimes in patients previously thought to be suffering from essential (or benign) hypertension. To that second group of cases the term ' malignant hypertension ' (Keith, Wagener, and Kernohan, 1928) has been given. Arguing from the contrasting clinical and patho-logical features of ' red ' and ' pale ' hypertension, Volhard has postulated a difference in the physiological mechanisms by which the two kinds of hyper-tension are produced; he attributes the rise of blood-pressure in ' red ' hypertension to diminished extensibility of the arteries produced by struc-tural changes in their walls, while in the ' pale ' variety the blood-pressure is raised by the vasoconstrictor action of a hypothetical pressor substance circulating in the blood. For some years his assistants (Hülse, Bohn) have sought experimental proof of the presence of this pressor substance. Bohn claims to have obtained such proof. He worked first (Bohn, 1931) with alcohol extracts of citrated plasma; after evaporation of the alcohol, the residue, taken up in saline and injected intravenously in curarized cats under urethane, produced a rise in blood-pressure. Later (Bohn, 1932) he pre-pared ultrafiltrates of the plasma, and, using the same cat technique, obtained a pressor effect with them. Control alcohol extracts from patients with normal blood-pressures or with essential (' red ') hypertension usually gave slight depressor effects; control ultrafiltrates did not alter the blood-pressure in either direction.

It is obvious that proof of Volhard's hypothesis would be a very important advance in the investigation of the problems of hypertension and nephritis, so important, indeed, that the evidence on which it rests calls for the strictest criticism and the amplest confirmation. The work on which this paper is

[1] Received November 10, 1934.

based was begun as an attempt at confirmation, but has ended in criticism of Bohn's methods and results.

Several accounts of attempts to repeat Bohn's work have already been published. These will not be discussed here in detail, but reference must be made to de Wesselow and Griffiths' paper (1934). Working chiefly with alcohol extracts, these authors entirely failed to confirm Bohn's observations; the present work, dealing mostly with ultrafiltrates, is complementary to theirs.

Methods

The technique described by Bohn (1931) was first repeated as closely as possible. Extraction of 30 c.c. of citrated blood with alcohol, evaporation of the alcohol, and suspension of the residue in a few c.c. of saline offered no difficulty. Testing the effect of this suspension on the blood-pressure of the cat, under urethane and curare, was not so straightforward. The significant pressor response which Bohn (1931) describes and illustrates (in uncalibrated tracings), is a rise of 10–20 mm. Hg. in the cat's blood-pressure, beginning shortly after the conclusion of the injection, reaching its maximum in three to five minutes, and passing off in five to ten minutes. Such a rise is demonstrable only in an animal whose blood-pressure, apart from injections, remains for long periods constant and free from fluctuations greater than, say, 5 mm. Hg. With urethane anaesthesia alone we seldom obtained the necessary freedom from minor fluctuations, and with the specimen of curare which we tried (on decerebrate cats) we found that a dose large enough to paralyse the muscles of respiration caused a pronounced fall in blood-pressure. After various trials we found that the steadiest tracings were obtained with the anaesthetic 'dial' (a preparation containing urethane, diallylbarbituric acid, and monoethyl urea), which we finally substituted for Bohn's urethane anaesthesia with curare.

During these preliminary experiments we tested extracts from eleven patients with 'pale' hypertension, and from nine controls, without obtaining even suggestive evidence of a consistent pressor activity in the former. The responses in the blood-pressure tracings were quite variable.

In 1932 Bohn as already mentioned, began to use ultrafiltrates of plasma instead of alcohol extracts, following closely the technique described by Anselmino and Hoffmann (1931). He claimed that a marked pressor effect was demonstrable with great regularity in ultrafiltrates from cases of 'pale' hypertension, but not in those from cases of 'red' hypertension. We therefore prepared and tested ultrafiltrates in place of alcohol extracts. The chief obstacle to the demonstration of a pressor effect of the order of 10 to 20 mm. Hg. was that the increase of circulating blood-volume caused by the injection itself produced a rise of blood-pressure. A similar rise could be produced by injecting normal saline. It varied widely from cat to cat and from time to time during an experiment on a given cat, and it was often

as great as 10 mm. Hg.; it was usually transient, but sometimes the tracing would continue at the higher level. We made various attempts to obviate the difficulty of this 'volume-effect'. It could be reduced by giving the injection very slowly, but prolongation of the injection time, even to many minutes, by no means abolished it. Concentration of the injection by evaporation was of no advantage, the osmotic effect of hypertonicity merely replacing the volume-effect. An arteriovenous anastomosis made of glass and having a capacity of 10 c.c. was tried. It was tied in position between the femoral artery and vein and filled with the saline or ultrafiltrate to be injected; when the vessels were unclamped, arterial blood entered the anastomosis and displaced the saline or ultrafiltrate into the vein, leaving the volume of fluid in the cat's vessels unaltered. With isotonic saline, however, this procedure always caused a transient fall in blood-pressure, due, no doubt, to the rapid removal of blood from the arterial side of the circulatory bed. It was therefore abandoned.

In the course of these attempts to eliminate the volume-effect, ultra-filtrates from seven more patients with 'pale' hypertension (with corresponding controls from normal persons) were examined; so far as could be judged from the results, there was again no consistent pressor activity in the former.

The problem at this stage was to demonstrate the pressor effect (if any) of an injection of ultrafiltrate, as distinct from its volume-effect. Since we had found no way of eliminating the latter, we decided to give all injections intravenously at a fixed rate, standardize our technique throughout, and treat the results in a quantitative and quasi-statistical manner. The full technique of the remaining experiments was therefore as follows:

Approximately 50 c.c. of blood from the patient's vein was withdrawn into a flask containing 2·5 c.c. of 4·5 per cent. sodium citrate solution. The plasma was separated by centrifugalizing, and acidified by adding 1 c.c. of normal acetic acid per 20 c.c. plasma (following Anselmino and Hoffmann (1931)). Ultrafiltration was then carried out without delay through a collodion membrane. The preparation of this membrane from alcohol-ether-acetic-acid collodion and the method of rapid ultrafiltration have been described by one of us in detail elsewhere (Holiday and Wilson (1933)). Using this method it was possible to obtain 20 c.c. of ultrafiltrate in half an hour, i.e. within one and a half to two hours of the removal of the blood from the patient. In every case the testing of the ultrafiltrate on a cat was completed within about five hours of obtaining the blood. For this purpose a cat, usually weighing 2 to 3 kg., was anaesthetized on a warmed table by the intraperitoneal injection of 0·8 to 1·0 c.c. per kg. of 'dial'; its blood-pressure was registered on smoked paper by a recording mercury manometer connected with a cannula in the carotid artery, and injections warmed to body temperature were given from a graduated syringe into the femoral vein. The injections were arranged in groups of three, each group consisting of ultrafiltrate, normal saline, and normal saline containing 0·1 unit of

'pituitrin' (Parke Davis), the latter serving as a measure of the sensitivity of the animal to a peripherally acting pressor substance. The volume of every injection was 4 c.c. per kg. of the cat's weight, and the rate of injection was uniform and approximately 8 c.c. per minute. When the blood-pressure tracing became reasonably steady and as nearly as possible horizontal, the first injection—normal saline—was given. Six to ten minutes later, when the effect had passed off, the same volume of ultrafiltrate, made neutral to neutral red by the addition of a few drops of sodium hydroxide solution, was injected, and after a similar interval came the injection of saline containing 0·1 unit of 'pituitrin'. About half an hour later the group of three injections was repeated, this time in the order, ultrafiltrate, saline, pituitrin-saline. That was the standard procedure, which was varied as little as possible, and occasionally supplemented by one or two later injections. After varnishing, the tracings were examined and measured ; at every injection, the initial mean blood-pressure, the duration of the injection, the maximum rise, its time, and the time occupied by the return to the initial level, were recorded.

Results

Almost without exception every injection produced a rise in the blood-pressure tracing, beginning early in the injection period and reaching a maximum about the end of the injection period or within the next few seconds ; usually the tracing returned gradually to its initial level in a further three to six minutes, but it sometimes remained above the initial level for a much longer period. Examples are shown in Plate 22, Figs. 1 and 2. The rises produced by pituitrin-saline were usually steeper in their onset than those produced by saline only, while those produced by ultrafiltrates might resemble, in shape as well as in size, either the saline or the pituitrin-saline effects. The height of the maximum rise was therefore chosen as the characteristic by which the effect of an injection could be judged. Any single measurement might be subject to error through a spontaneous fluctuation in the blood-pressure, or through a slight spontaneous drift either upward or downward, but in the average value of a series such errors should cancel one another. Table I shows the measurements obtained in eleven experiments on nine cases of malignant hypertension ; lest any doubt should arise as to the clinical nature of these cases, summaries of them are given in the appendix. The 'volume-effects' produced by saline alone varied from 0 to 20 mm. Hg. rise in blood-pressure, and averaged 10·1 mm. 'pituitrin', 0·1 unit, in the same volume of saline, produced rises of 9 to 33 mm. Hg., averaging 18·6 mm. The ultrafiltrates produced rises which varied widely, from 3 to 28 mm. and averaged 13·4 mm. The series contains individual observations, such as that shown in Plate 22, Fig. 2, which might be offered as evidence of the presence of a pressor substance in the ultrafiltrate, but these are in the minority, and the difference between the average values 13·4 and 10·1 is so small as to be of doubtful significance. Table II

shows the measurements obtained in a control series of nine patients with normal blood-pressures. The saline and the pituitrin effects, in their range and their average values, closely resemble those of Table I; and, further, the ultrafiltrates from patients with normal blood-pressures produce just the

TABLE I

Exp. Case No.	Sex.	Age.	B.P.	Diagnosis.	Saline.	Saline plus 0·1 unit 'pituitrin'.	Ultra-filtrate.
				Patients.		Rise of cat's B.P. (in mm. Hg.) produced by 4 c.c./kg. of	
1 (a)	M	39	225/150	Malignant hypertension	14	—	13
					10	12	14
					9	—	16
1 (b)			220/160		10	—	12
					6	14	14
					5	—	—
					9	—	6
2	M	24	205/140	Malignant hypertension	9	20	16
					10	22	20
					—	—	15
3 (a)	M	48	175/120	Malignant hypertension	20	20	20
					16	20	28
3 (b)			180/120		12	23	19
					10	22	17
					10	—	—
4	M	53	215/120	Malignant hypertension	12	26	12
					14	28	12
					18	—	16
5	M	28	174/114	Malignant hypertension	5	12	8
					12	20	10
6	F	55	242/120	Malignant hypertension	16	16	16
					8	18	9
					7	—	10
7	M	59	230/140	Malignant hypertension	12	—	—
					10	33	20
					17	—	—
8	M	30	210/140	Malignant hypertension	4	14	11
					6	12	10
					4	—	3
					0	—	—
9	M	58	179/84	Malignant hypertension	15	13	7
					4	9	8
				Average	10·1	18·6	13·4

same variety of effects as those from the hypertensives of Table I, and a very similar average value (12·5 mm. Hg.). Neither by inspection of the tracings nor by these detailed measurements can any characteristic difference be found between the series of patients with malignant hypertension and the series of controls with normal blood-pressures.

Discussion

These experiments have failed to demonstrate Bohn's pressor substance. This may possibly be due to discrepancies between our technique and his, which is most fully described in his later paper (Bohn and Schlapp).

These discrepancies must therefore be discussed.　Our ultrafiltration was carried out like Bohn's with citrated plasma acidified as described by Anselmino and Hoffmann, and the time between removal of blood and testing of ultrafiltrate was certainly as short as his.　His filters, however, were porous porcelain pots impregnated with collodion from an acetic acid collodion solution.　Through clean pots freshly impregnated he failed to obtain active ultrafiltrates ; the pressor activity appeared only in filtrates from pots that had been used several times without being cleaned.　This finding he attri-

TABLE II

| Exp. Case No. | Patients. | | | | Rise of cat's B.P. (in mm. Hg. produced by 4 c.c./kg. of | | |
	Sex.	Age.	B.P.	Diagnosis.	Saline.	Saline plus 0·1 unit 'pituitrin'.	Ultra-filtrate.
10	M	63	110/90	Duodenal ulcer	12	31	5
					19	—	10
					19	29	17
11	F	28	120/85	Myasthenia gravis	9	19	2
					8	—	5
					8	17	5
12	M	25	125/85	Pleural effusion	3	16	9
					14	15	14
					5	—	8
13	M	53	140/90	Sciatica	17	18	13
					14	20	12
14	M	54	125/80	Dyspepsia	5	24	20
					9	17	20
15	M	47	150/100	Amoebic hepatitis	8	14	5
					10	13	10
16	M	21	120/80	Sciatica	15	24	26
					12	21	30
					12	—	31
17	M	46	120/80	Duodenal ulcer	8	15	7
					12	15	10
18	M	48	130/80	Duodenal ulcer	4	19	8
					6	24	9
				Average	10·4	19·5	12·5

butes to the adsorption of pressor substance up to saturation point in the thick layer of collodion through which the filtrate must pass.　Such adsorption is likely to occur only to a limited degree in our very thin membranes prepared from alcohol-ether-acetic-acid collodion ; indeed if, as Bohn (1932) suggests, the pressor substance resembles posterior pituitary hormone in its properties, it will probably not be adsorbed at all, for one of us has shown (Byrom and Wilson (1934)) that ' pituitrin ' passes through these membranes without loss of its antidiuretic potency.　In testing the ultrafiltrates on cats our technique differed from Bohn's chiefly in the use of ' dial ' instead of urethane and curare ; it is perhaps arguable that ' dial ' may inhibit the hypothetical pressor substance, but it is clear that it does not inhibit pituitrin.　A further discrepancy is that we did not insist, as he does (Bohn and Schlapp (1934)) that the initial blood-pressure level, when an injection is given, should always lie between 100 and 130 mm. Hg.　In most of our cases

it lay between 100 and 150 mm. Hg., and in a few it was as high as 170 or as low as 80. When the rises in blood-pressure produced by the saline injections and by the pituitrin injections are plotted against the corresponding initial levels (Fig. 3), the points are found to be widely scattered ; with the saline injections there is practically no tendency for smaller rises to occur at higher initial levels, while with the pituitrin-saline injections such a tendency is present, but slight. If the hypothetical pressor substance has a mode of action even remotely resembling that of pituitrin, it is clear from

FIG. 3.
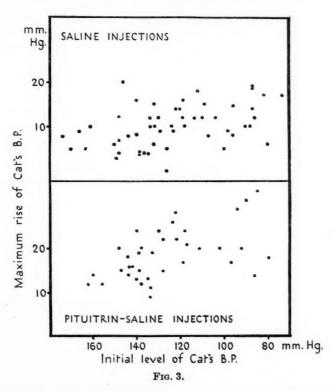
Fig. 3 that its average effect will be very nearly as great when the blood-pressure at the time of injection lies between 130 and 160 mm. Hg. as when it lies between 100 and 130 mm. Hg.

It seems very unlikely then that these slight discrepancies in technique are the reason for our failure to confirm Bohn's findings. Since every ultra-filtrate injection was controlled by an injection of saline and another of pituitrin as near to it in time as possible, and since every response was measured and recorded, the results of these experiments have a greater claim to accuracy than Bohn's published results ; for he enters his findings merely as ' positive ' or ' negative ', he does not seem to have controlled his technique so rigidly, and he does not appear to have experienced difficulty with a

' volume-effect ' produced by the injection of saline only.   In spite of this greater accuracy, our experiments have furnished no evidence of a pressor substance in ultrafiltrates from the blood of patients with ' pale ' hypertension.   This might possibly be discounted on the ground that we have examined only nine cases, Bohn many times that number.   We should have extended our series, however, had we not become convinced that the whole method, both as used by us and as described by Bohn, is not adequate to its purpose.   If 10 c.c. of ultrafiltrate, representing say 20 c.c. of blood, is injected into the vein of a 2·5 kg. cat, it will be diluted in a few seconds to approximately 200 c.c. ; any pressor substance present will reach the cat's arterioles in a concentration not greater than one-tenth of that originally present in the human blood, and even this fraction will be reduced by incidental losses and diffusion out of the cat's blood-stream.   It seems theoretically unlikely that this concentration of pressor substance would produce a clear-cut effect on the cat's blood-pressure.   In practice, even if it did produce an effect represented by a 10 to 20 mm. rise, this is too close to the border-line of the experimental error of the method to be shown clearly in single experiments.   For these reasons we feel that further use of the method is unprofitable, and that Bohn's demonstration of the presence of a pressor substance in plasma ultrafiltrates from patients with ' pale ' hypertension is not convincing.   It appears indeed from the paper of Bohn and Schlapp (1934), published after the present work was concluded, that Bohn himself failed to repeat his own results on ultrafiltrates, and turned his attention back to alcohol extracts.

Summary

An attempt has been made to confirm Bohn's claim that a pressor substance can be demonstrated in the ultrafiltrates from the plasma of patients suffering from Volhard's ' pale ' hypertension.   Bohn's technique (ultrafiltration through collodion and testing the effect of ultrafiltrate on the cat's blood-pressure) has been followed closely, though not exactly.   The results showed no satisfactory evidence of a pressor activity in the blood of nine such patients.   The limitations of the method make it unsuitable for the detection of pressor substance in the amounts which Bohn claims to have demonstrated.

APPENDIX.   *Case Records.*

Case 1. C. B., male, aged 39, a butcher, was admitted into hospital in July 1933 complaining of morning headache, occasional vomiting, and increased frequency of micturition with some increase in the amount of urine passed. These symptoms had been present for ten months. Five months before admission he had noticed misty vision in the right eye for several days.

On examination he appeared well-nourished and of good colour. The significant findings were cardiovascular hypertrophy with raised blood-pressure (240/160); slight bilateral papilloedema, apparent marked narrowing of the retinal arteries, a small haemorrhage in the left optic disc, and an area of creamy white exudation and an early macular star figure in the right fundus; no anaemia; a cloud of albumen in the urine, with many red cells and occasional leucocytes in the urinary deposit; slight polyuria, and possibly slight impairment of renal efficiency (blood urea, 0·042 per cent., 0·049 per cent., phenol-sulphonephthalein excretion 33 per cent. in two hours, van Slyke's 'standard clearance' of urea 48 per cent. to 61 per cent. of normal).

Experiments 1 (*a*) and 1 (*b*) were made at this time.

The patient was discharged from hospital. Six months later he was re-admitted with acute heart failure and great impairment of renal efficiency and died. There were macular star figures in both retinae, and a haemorrhage in the left disc. Permission for post-mortem examination was refused.

Diagnosis: Malignant hypertension.

Case 2. M. G., male, aged 24, a salesman, was admitted into hospital in June 1933 complaining of morning headache, giddiness, blurring of vision, shortness of breath, and slight polyuria. These symptoms had been present for six months, and followed an illness which involved pain in the side and in the joints and was labelled ' pleurisy and rheumatism '.

On examination he appeared pale and rather thin. The significant findings were cardiovascular hypertrophy and raised blood-pressure (200/140); bilateral papilloedema, flame-shaped retinal haemorrhages and areas of exudate and macular star figures in both retinae; anaemia (4,000,000 red cells, 50 per cent. haemoglobin (Dare)); a heavy cloud of albumen in the urine, with red cells and casts; and some impairment of renal efficiency (blood urea 0·082 per cent., phenol-sulphonephthalein excretion 20 per cent. in two hours, van Slyke's ' standard clearance ' of urea, 26 per cent. of normal).

Experiment 2 was made at this time.

Diagnosis: Malignant hypertension.

Case 3. R. C., male, aged 48, a tailor's presser, was admitted into hospital in July 1933 complaining of intermittent attacks of pain in both groins, radiating to the right loin and to both testicles, lasting from several hours to a week at a time; also of morning headache, marked shortness of breath on exertion, palpitation, giddiness, increased frequency of micturition, and deterioration of vision chiefly in the right eye. These symptoms had been conspicuous for two years. Three years before admission he had been operated on for the radical cure of bilateral inguinal herniae, which for some years previously had been associated with pain in both groins and testicles.

On examination he appeared well-nourished, and in fairly good general condition. The significant findings were cardiovascular hypertrophy, with

high blood-pressure (220/125, falling to 175/120 in bed); signs of chronic bronchitis; moderate papilloedema in both eyes, more marked in the right, with scattered haemorrhages, sometimes associated with creamy-white areas, and in the left macula an area of granular choroidal degeneration; slight anaemia (5,400,000 red cells; 65 per cent. haemoglobin (Dare)); a trace of albumen in the urine, no fixation of specific gravity; no impairment of renal function.

Experiments 3 (*a*) and 3 (*b*) were made at this time.

Three months later slight papilloedema was recorded again, with numerous haemorrhages in the right eye and an early star figure at the right macula.

Histological examination of a portion of the right kidney made six months later showed the changes characteristic of nephritis repens (Russell, 1929).

Diagnosis: Malignant hypertension.

Case 4.   S. C., male, aged 53, a pepper and spice miller, was admitted into hospital in July 1933 complaining of morning headache, sometimes with vomiting, shortness of breath on exertion, giddiness, increased frequency of micturition, and intermittent oedema of feet. These symptoms had been present for about a year, prior to which he had suffered for six years from dyspeptic symptoms suggestive of peptic ulcer. Two months before admission he vomited a quantity of blood.

On examination he appeared well-nourished but pale. The significant findings were cardiovascular hypertrophy with raised blood-pressure (215/120); a few basal crepitations; tenderness over the liver below the right costal margin; anaemia (5,000,000 red cells, 50 per cent. haemoglobin (Dare)); apparent pronounced narrowness of the retinal arteries and one small haemorrhage in the left retina; fixation of the specific gravity of the urine between 1,010 and 1,014; moderate albuminuria, with at times a positive guaiac reaction; and some impairment of renal efficiency (blood urea 0·073 per cent., van Slyke's 'standard clearance' of urea 39·9 per cent. of normal).

Experiment 4 was made at this time.

Two months after this several more haemorrhages had appeared in the right retina and optic disc, and five months later early papilloedema was first observed, with still more retinal haemorrhages and the beginning of a star figure. Ill health, headache, shortness of breath, and frequency of micturition continued; the hypertension, and the urea retention in the blood showed little change.

Diagnosis: Malignant hypertension.

Case 5.   H. L., male, aged 28, a contractor, was admitted into hospital in November 1933 complaining of headache of increasing severity for seven months, polyuria for two months, and misty vision for three weeks.

On examination he appeared moderately stout and florid. The significant findings were slight cardiovascular hypertrophy with raised blood-pressure (190/130); bilateral papilloedema, with numerous haemorrhages and some areas of creamy exudate in both retinae, and macular star-figures; moderate albuminuria, with red cells in the urinary deposit; no anaemia; slight polyuria (80–90 oz. in 24 hours) and a tendency to fixation of the specific gravity of the urine; blood urea normal (0·027 per cent.).

Four weeks after admission he had an attack of hypertensive encephalopathy, from which he recovered after venesection and the administration of morphia. His condition then showed little change up till the time experiment 5 was made, eleven weeks after admission.

He was discharged, and readmitted a month later on account of abdominal pain and headache. His condition rapidly deteriorated. Anaemia and renal failure developed, and he died in three weeks. Post-mortem examination showed nephritis repens (Russell, 1929), cardiovascular hypertrophy, subarachnoid haemorrhage, and an adenoma in the anterior lobe of the pituitary.

Diagnosis : Malignant hypertension.

Case 6. E. H., female, aged 55, housewife, was admitted into hospital in January 1934 complaining of discomfort in the head and giddiness of six years' duration, swelling of the legs for over a year, and shortness of breath with cough and bloodstained sputum for a month following an attack of ' congestion ' of the lungs. Six years previously her doctor had told her that her blood-pressure was 250. She also complained of deafness and recent impairment of vision.

On examination she appeared pale and ill. The significant findings were marked cardiovascular hypertrophy with raised blood-pressure (230/130) ; slight oedema of shins and back ; crepitations at the bases of the lungs and some enlargement of the liver ; bilateral slight to moderate papilloedema with numerous and extensive retinal haemorrhages but no exudate ; anaemia (4,000,000 red cells, 47 per cent. haemoglobin (photo-electric method)) ; considerable albuminuria, with red cells and occasional casts in the urine ; and marked impairment of renal efficiency (relative fixation of specific gravity of the urine about 1,010 ; blood urea 0·277 per cent. ; phenolsulphonephthalein excretion, a trace in two hours: van Slyke's ' standard clearance ' of urea 4 per cent. to 5 per cent. of normal).

Experiment 6 was made at this time.

Diagnosis: Malignant hypertension.

Case 7. F. W., male, aged 59, a dock labourer, was admitted into hospital in March 1934 complaining of shortness of breath especially at night, cough, increased frequency of micturition, shooting pains in arms and legs, and loss of three stone in weight. These symptoms had been present for eight months.

On examination he appeared well nourished and of good colour. The significant findings were cardiovascular hypertrophy with raised blood-pressure (285/150) ; clinical and radiological evidence of chronic bronchitis and emphysema with some fibrosis and pleural thickening in the right lung ; slight bilateral papilloedema, numerous small scattered haemorrhages in both retinae, and a few small white glistening areas of exudate in the region of the left macula ; no anaemia ; considerable albuminuria (one-third volume), with many red-blood cells in the urinary deposit ; marked impairment of renal efficiency (blood urea 0·102 per cent., phenolsulphonephthalein excretion a trace only in two hours, van Slyke's ' standard clearance ' of urea 9 per cent. of normal).

Experiment 7 was made at this time.

Diagnosis : Malignant hypertension.

Case 8. W. W., male, aged 30, a labourer, was admitted into hospital in April 1934 complaining of shortness of breath and intermittent headache for two to three years and defective vision for three months. Nine years previously he had vomited blood, and since then had suffered from mild irregular dyspepsia.

On examination he appeared healthy. The significant findings were

moderate cardiovascular hypertrophy with raised blood-pressure (175/100); slight papilloedema in the right eye, small haemorrhages and areas of creamy exudate in both retinae, and an early macular star in the left; no anaemia; considerable albuminuria, with a few leucocytes and red cells in the urinary deposit; slight impairment of renal function (fixation of the specific gravity of the urine between 1,008 and 1,012, blood urea 0·04 per cent., phenol-sulphonephthalein excretion 36·4 per cent. in two hours, van Slyke's 'maximum clearance' of urea 44 to 46 per cent. of normal).

Experiment 8 was made at this time.

Diagnosis: Malignant hypertension.

Case 9. W. H., male, aged 58, a stoker, was admitted to hospital in May 1934 complaining of shortness of breath, cough with white, sometimes blood-stained sputum, nycturia, and loss of weight. These symptoms had been present for six weeks; for two days his ankles had been greatly swollen.

On examination he appeared ill, with a pale greyish complexion, slight yellowish-brown pigmentation, and orthopnoea. The significant findings were cardiovascular hypertrophy with raised blood-pressure (210/140); cardiac failure (gross oedema of lower limbs and lower trunk, enlarged liver, left pleural effusion, and numerous basal crepitations); bilateral papilloedema, and extensive retinitis with haemorrhages and areas of exudate; anaemia (4,000,000 red cells 61, per cent. haemoglobin (photo-electric method)); moderate albuminuria with many red cells in the urinary deposit; and marked impairment of renal efficiency (fixation of specific gravity of the urine between 1,006 and 1,012, blood urea 0·146 per cent., phenolsulpho-nephthalein excretion 18 per cent. in two hours, van Slyke's 'standard clearance' of urea 18 per cent. of normal).

The signs of heart failure disappeared with rest in bed, but the hypertension and renal insufficiency persisted. Experiment 9 was then made.

Diagnosis: Malignant hypertension.

REFERENCES

Anselmino, K. J., and Hoffmann, F., *Klin. Wchnschr.*, Berl., 1931, x. 1438.

Bohn, H., 1931, *Ztschr. klin. Med.*, Berl. 1931–2, cxix. 100.

Bohn, H., 1932, *Verh. d. deutsch. Ges. Kreislaufforsch.*, v. Tagung, Dresden, 1932, p. 112.

Bohn, H., and Schlapp, W., *Ztschr. klin. Med.*, Berl., 1934, cxxvii. 233.

Byrom, F. B., and Wilson, C., *Quart. Journ. Med.*, Oxford, 1934, iii. 361.

Hülse, W., *Ztschr. f. d. ges. exp. Med.*, Berl., 1924, xxxix. 413.

Keith, N. M., Wagener, H. P., and Kernohan, J. W., *Arch. Int. Med.*, Chicago, 1928, xli. 141.

Russell, Dorothy S., *A Classification of Bright's Disease*, Med. Res. Council Spec. Rep. Ser., 142, Lond., 1929.

Volhard, F., *Handbuch der Inneren Medizin*, Bergmann und Staehelin, Berl., 1931, vi. part 1.

de Wesselow, O. L. V. S., and Griffiths, W. J., *Brit. Journ. Exper. Path.*, Lond., 1934, xv. 45.

Wilson, C., and Holiday, E. R., *Biochem. Journ.*, Cambridge, 1933, xxvii. 1095.
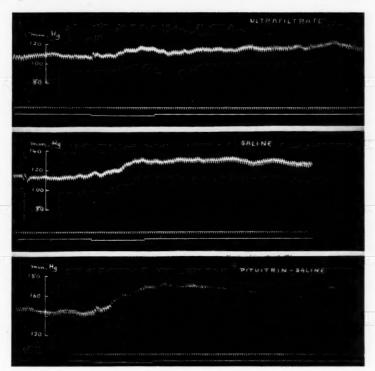
FIG. 1.   From Exp. 4 (Case 4): Cat, female, 2·2 kg., anaesthetized with 1·75 c.c. 'dial' intraperitoneally; record of carotid blood-pressure.   *Signal line*: duration of injection (8·8 c.c. on every occasion) into femoral vein.   *Time-trace*: 2-second intervals.
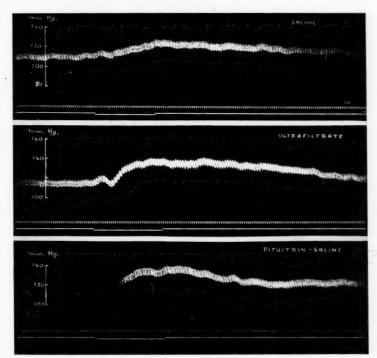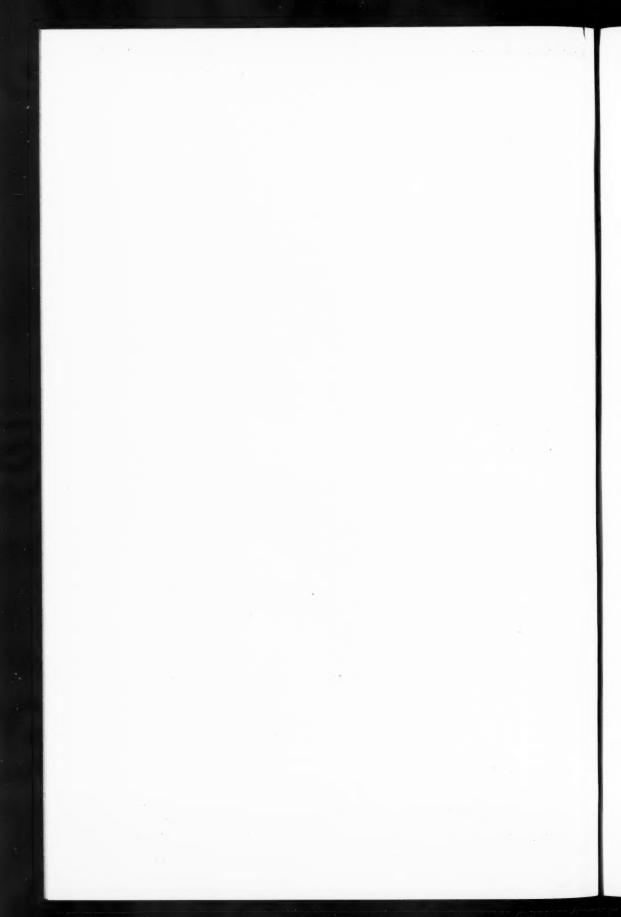
FIG. 2.   Exp. 3 (*b*) (Case 3): Cat, male, 2·6 kg., anaesthetized with 2·1 c.c. 'dial' intra-peritoneally; record of carotid blood-pressure.   *Signal line*: duration of injection (10·4 c.c. on every occasion) into femoral vein.   *Time-trace*: 2-second intervals.

616.398

SECONDARY PELLAGRA [1]

By S. LEVY SIMPSON

With Plates 23 to 25

PELLAGRA is a disease generally held to be of nutritional origin, and characterized by dermatological, gastro-intestinal, and nervous manifestations; it occurs extensively in maize-eating communities, but also sporadically in all parts of the world, and especially in asylums. Its diagnosis depends largely upon the character of the skin lesions, which are described below. The occurrence of pellagra in England has been summarized by Bigland (6) and by Stannus and Gibson (30). The latter authors, and Biggam and Ghallionni (5) have recently described its clinical features and pathology. Chick (9) has considered the conflicting views on the aetiology of pellagra, and has endeavoured to harmonize some of them as follows: 'Pellagra is caused by a toxic substance derived from the maize diet, which can be corrected by sufficient "good" protein, or perhaps by sufficient vitamin B_2 (which is found to accompany the "good" proteins).'

The present contribution deals with a condition known as 'secondary pellagra', that is, pellagra occurring secondary to an initial gastro-intestinal lesion or disorder, the causation of which is entirely unconnected with pellagra. According to this definition, 'secondary pellagra' is comparable to the megalocytic hyperchromic anaemias that have been described as resulting from gastrectomy and other gastro-intestinal lesions (Wilkinson (37), Ungley (36), Rowlands and Levy Simpson (19), &c.).

In 1916 Rolph (25) described a case of 'Cancer of the Stomach and Pellagra occurring in the same patient'. He was the first to consider a possible connexion between the two conditions. Three years later Bryan (7) recorded a case of 'Cancer of Stomach with associated Pellagra'. In 1925 Bender (3) described three cases of 'Pellagra secondary to lesions of the stomach interfering with nutrition'. His paper indicates clearly for the first time the sequence of events and the apparent gastro-intestinal contributing cause of the pellagra. Especially is this true of one of his patients who developed pellagra while being fed through a jejunostomy tube for the cure of a non-malignant gastric ulcer. The other two patients had carcinoma of the stomach.

In 1926 O'Leary (23) described five cases of secondary pellagra, two following gastro-enterostomy for gastric and duodenal ulcer, one of carcinoma of the

[1] Received January 21, 1935.

stomach, one of carcinoma of the colon, and one of stricture of the oeso-
phagus.   O'Leary wrote : ' The term " secondary pellagra ' might aptly be
applied to such cases to distinguish them from those in which there are
symptoms and signs of pellagra, but no evidence of organic disease in the
gastro-intestinal tract.'   In the same year Barnes (2) recorded ' Typical pel-
lagra syndrome developing in a patient with chronic ulcerative colitis ' ; and
in 1930 Ellis (11) noted the occurrence of pellagra secondary to tuberculous
enterocolitis with severe diarrhoea in a boy of 9.   Turner (35) described
sixteen cases, eight of which had stricture of the rectum.   Eusterman and
O'Leary (12) in 1931 added thirteen cases, including instances of malfunction-
ing gastro-enterostomy, jejunal feeding, and gastric syphilis.   They also stated
that ' the continued use of alcohol over a period of several weeks or months
favours the development of the secondary form of the disease through gastro-
intestinal upsets, anorexia and eventual semi-starvation '.   Minot, Strauss,
and Cobb (21) found that fourteen of fifty-seven patients suffering from
alcoholic polyneuritis ' had dermatitis and other lesions characteristic of
pellagra '.   In a more recent paper Strauss (31) stated that ' deficiency
disease in man may, and frequently does, develop because of some dis-
turbance of the gastro-intestinal tract in spite of an apparently adequate
diet '.

Up to 1932 it would appear that ' secondary pellagra ' was a disease almost
confined to America and Canada, but in that year Thaysen (33) reviewed
the literature and described two of his own cases.   His contribution made the
condition more familiar to physicians on the Continent, but even up to the
present time only a sprinkling of cases have been recorded in Europe,
a recent publication being that of Morawitz and Mancke (22).   Although
the conception of ' secondary pellagra ' has not been described as such in
England, the present writer has found two descriptions which justify inclu-
sion under this heading. In 1926 Hutchison and Patterson (18) described two
examples of ' Pellagra in Children in England ', one of which was a girl of 10
years old, who first manifested pellagra at the age of 3 or 4, but ' as a baby
she had intractable diarrhoea, since when she had always had to " leave the
table in a hurry ".   Her bowels were inclined to be especially loose in the
summer ' ; and in 1932, Bennett, Hunter, and Vaughan (4), in an article on
' Idiopathic Steatorrhoea (Gee's disease) ' described pellagra-like lesions in
two cases : ' In Case 13 there was a patch of pellagra-like pigmented erup-
tion over the left ankle.   In Case 8 the skin condition was so severe as to be
the presenting symptom on admission to hospital.   There were large, moist,
red, abraded areas, from 2 cm. to 8 cm. diameter, on all limbs and to
a lesser extent on the trunk.   Many of these lesions showed scaly-brown
pigmented borders ; one on the calf had a deep brown scaly periphery and
a moist, red, abraded centre, the whole appearance being not unlike pellagra.
The condition cleared up within three weeks, when the patient was given
large doses of marmite on account of her severe megalocytic anaemia.
The improvement in the skin condition, which was as striking as that

in the blood, was probably due to the rich vitamin B content of the marmite.'

In 1933 the writer briefly referred to the case described in detail below when dealing with 'secondary pellagra' in a discussion on pellagra at the Royal Society of Medicine (19).

Case Report

The patient, a spinster aged 46, was sent to see the writer in consultation on 5th September 1933; the symptoms of weakness, lassitude, loss of weight, and depression, and the presence of pigmentation having suggested to her family doctor the possibility of Addison's disease. In September 1931 a two-thirds gastrectomy had been performed on the Continent for a duodenal ulcer. For several years previous to this operation she had suffered periodic attacks of dyspepsia, their character being in keeping with, although not completely characteristic of, the lesion said to have been found on laparotomy. However, all dyspeptic symptoms, except occasional flatulence, ceased after operation.

In March 1932 the patient began to notice a lack of energy and a progressive weakness and loss of weight, the latter amounting to 28 lb. in the next eighteen months. In the spring and summer 1933 some darkening of the face and dryness of the backs of the forearms occurred. There was little tendency on the part of the patient to stress the dermatological aspects, although to the observer they appeared to be the most striking feature. In response to questions the patient stated that her skin had been rather dry for two years, but more so during the past year. She had not particularly noticed the changes in the skin of the neck, and had ascribed these and those on the leg as due to sunburn. She did, however, then ask: 'Why do my arms and hands look like those of an old sea captain?' A sensation of pins and needles in the hands was experienced in May 1933, and towards the end of the summer soreness of the tongue was complained of.

In 1933 mental and emotional changes were observed by the patient and her relatives, so that she became a somewhat 'difficult' person to live with. Depression, amounting at times to melancholia, indecision, anxiety, and contrariness appeared to be the worst features; the following quotations of the patient's own remarks give a more vivid account: 'Up against a blank wall, literally not knowing what to do next; utter lack of concentration, not able to write letters or grasp the meaning of the lightest book; dread of losing things, constant searching among absolutely tidy drawers, bookshelves, and writing tables; breakdown of speech and inability to grasp what is being said to me; indecision as to what is put on every day; increased feeling of helplessness and incompetence, literally reduced to state of infancy, hands refusing to do the simplest jobs.'

There had been a tendency to constipation for some years, and no marked change had occurred in the past two years. Menstruation commenced at the age of 13, and occurred regularly every four weeks, lasting for five days. For a few years previous to operation the duration of bleeding had increased to some nine days, but after the gastrectomy there had been amenorrhoea for six months, and subsequently very scanty menstruation lasting only one or two days, but occurring regularly every four weeks. (A similar apparent

sequence to gastrectomy has been noted by Rowlands and Levy Simpson (27) and its specificity queried. An alternative explanation is influence of shock that might occur with any severe operation. The time sequence appears to exclude anaemia as the cause of the amenorrhoea.)

There was no additional previous history of importance. The patient came from pure Cornish stock, tracing her ancestors through several generations, and, apart from holidays in Europe, had lived in England all her life.

The patient had been a vegetarian since 1919, eating no meat or fish. Her daily dietary included half pint of milk, 2 oz. cream, cheese, and plenty of fresh fruit and vegetables; three eggs were taken per week; 'barley kernels' were consumed for breakfast on a liberal scale. In May and June of the year 1933, however, the patient lived in an institution where all ills were cured by drastic limitation of diet, fruit only being allowed for some weeks. She returned to her usual diet on leaving the institute.

Examination 5th September 1933. The patient was an extremely intelligent and cultured woman, very rational, but manifesting considerable anxiety. She was tall (5 ft. 10 in.), sparse, active, and alert. The neck and forearm distribution of the skin lesions, as well as their character (Plate 23, Figs. 1*a*, 2*a*, Plate 24, Fig. 3*a*), immediately brought to mind examples of pellagra that the writer had seen in America. By the courtesy of Dr. Hamilton Fairley, whom the writer asked to confirm the diagnosis, an extract from his description of the lesions is included : ' There was a brown pigmentation and thickening of the dermis with patches of atrophy and wrinkled, elastic, thin skin over the neck and front of the chest. The rash was symmetrical and in places showed a definitely pigmented border similar to the hyperkeratotic border of Merk. There was a butterfly distribution of bronzing over nose and face. A pellagrous rash involved the back of the hands and forearms, the dorsum of the feet, and the front of the legs. The skin generally tended to be dry, and some yellowness was present, but there was no abnormal pigmentation around the anus, vulva, axillae, or nipples.'

Apart from the more typical lesions, the face and neck were somewhat diffusely brown ; the abdomen, lower chest, and nipples were completely free from increased pigmentation, as was also the linea alba, and the scar of the operation. The lower dorsal spine showed brown pigmentation, and two symmetrical patches of pigmentation and keratosis were present over the ischial tuberosities. The skin covering the anterior surface of the legs was very glossy and thin with a marked tendency to crack. The pigmentation and keratosis of the feet (Plate 24, Fig. 3*a*) were sharply demarcated at a line where the sandals had permitted exposure to the sun.

The tongue was denuded of filiform papillae in its anterior two-thirds, being smooth and pale, but the posterior third was covered with white fur. The roof and floor of the mouth had a yellowish pigmentation such as is seen in carotinaemia, but the palms of the hands were not similarly affected. The lips were pallid and somewhat cyanotic. At the lateral angles of the mouth there were some cracks and fissures which the patient had been unable to heal with ointment, and which Dr. Stannus found to be quite typical of pellagra. The tonsils were not enlarged, and there was no enlargement of cervical glands. The thyroid gland was just palpable, but no signs of hyperthyroidism were present. The systolic blood-pressure was 120, the diastolic 90 mm. of mercury. The pulse was 80, and the respirations 20. The apex beat was half an inch internal to the nipple line and the heart sounds normal in intensity and rhythm. The respiratory system was normal. Palpation of the abdomen revealed no abnormalities. No oedema

of the legs was present. Examination of the nervous system gave no objective evidence of subacute combined degeneration; the knee jerks and ankle jerks were brisk and equal, and the plantar responses, postural sensibility, sensation and vibratory senses normal.

The patient was admitted to the London Hospital on 20th September 1933 for further investigations. Her weight on admission was 113 lb. She was very depressed, and tended to cry on slight provocation. Clinical examination revealed no marked difference from the findings at the initial examination on 5th September. No treatment had been undertaken in the interval.

The photographs (Plate 23, Figs. 1a, 2a, Plate 24, Fig. 3a) show the condition of the skin on admission. Dr. W. O'Donovan and Dr. A. Burrows kindly confirmed their identity with pellagra lesions. A piece of skin was taken from the forearm on 22nd September, and Dr. W. W. Woods reported on the microscopic sections (Plate 24, Fig. 4): 'Hyperkeratosis; considerable pigmentation of basal layer of epidermis.' A blood count (Dr. P. N. Panton) showed a severe microcytic anaemia : erythrocytes 2,600,000, haemoglobin 26 per cent., colour index 0·5, leucocytes 4,400; polymorphonuclear 63·5, small lymphocytes 26, large lymphocytes 7, large hyaline 2·5, basophil 1, reticulocytes 1·4 per cent.; red cells pale, considerable poikilocytosis, anisocytosis, and polychromatophilia; 2 normoblast seen in counting 200 white cells. Test meal showed achlorhydria, and a low total acidity 20 to 30 c.c. of decinormal H.Cl. per 100 c.c. test meal; pepsin was, however, present.

Radiography of the gastro-intestinal tract was carried out by Dr. C. A. Withers: 'Oesophagus clear; the barium passed into the upper part of the stomach without delay. Only half the stomach was seen, and the barium passed via the stoma into the first coils of the jejunum. After one hour a normal appearance of the small gut was seen; after five hours the food had reached the caecum.'

The plasma proteins (J. R. Marrack) were definitely low, 5·6 per cent. compared with the normal of about 7 per cent. This significant reduction of plasma proteins was not associated with any oedema. The plasma carotin (J. R. M.) was high, 0·2 mg. per 100 c.c. as compared with the normal 0·04 to 0·08 mg. This was in keeping with the yellow discoloration of the palate and the vegetarian diet. The direct Van den Bergh reaction was negative and the indirect normal, being less than 0·2 mg. per cent. The Wassermann reaction was negative. The blood urea and the urine were normal. The diastatic index was 20. The serum calcium was 9·2 mg. per 100 c.c. and the plasma phosphorus 3·75 mg. per 100 c.c. The stools contained 22·2 grm. per cent. of total fat, of which 56·8 per cent. were saponified, 3·6 per cent. neutral fat, and 6 per cent. free fatty acid, all figures being within normal limits. An investigation of the inorganic and ethereal sulphates (J. R. M.) showed no gross abnormality.

Intestinal absorption-tests, kindly carried out by Dr. Peter Meyer, indicated impaired or delayed absorption. The rate of absorption was estimated by the time which passed before ingested methylene-blue was excreted in the urine : whereas with normal patients a considerable amount of methylene-blue appears in the first or second hour after ingestion; in this case only traces were found within three hours.

Dr. D. C. Carroll kindly visited the patient to form an opinion on the psychological aspects, and reported that : 'She had a definite "depressive state". The depression was of moderate severity marked by pessimism about the present and future and by mildly self-reproachful ideas about the

past. She thought seriously about suicide, though she felt it unlikely that she would attempt it. She was over-critical of herself, and was morbidly sensitive to the opinions of others and felt that people were critical of her, though not to the extent of having true ideas of reference. She was quite friendly in attitude to me, but felt certain people were unfriendly. There was very slight retardation of ideation. There was considerable doubt in her mind about all decisions. There was considerable anxiety accompanied by mild agitation and much obsessional thinking with a very few compulsive actions relating to ideas of contamination. Confusion was very slight. There was slight loss of memory for recent events. Intelligence was unimpaired. Orientation was normal. There were no delusions or hallucinations.'

Treatment. In view of the definite dermatological lesions this patient appeared to be suitable for testing the effects of vitamin B_2, and for this purpose Dr. Lucy Wills and Dr. Harriette Chick were consulted. It was decided to leave the diet of the patient during the test period the same as she had been having during the past year or so, and to postpone the administration of iron. The only alteration in the regimen was the addition of a preparation free from coagulable proteins and made from egg white by Dr. Chick and her co-workers at the Lister Institute. This extract contained a high concentration of vitamin B_2, but was entirely free from B_1. The daily rat dose of the extract was found to be $0.5-1.0$ c.c., which was equivalent to $5.0-10.0$ grm. of the original egg white. Commencing on 23rd September, 100 c.c. of the egg white preparation was given by mouth twice daily for a period of fifteen days. The apparent effect on the skin was remarkable. By the end of the first week there was considerable diminution of hyperkeratosis and pigmentation, and by the end of the second week there was superficially a close approximation to normal, as is shown by the photograph (Plate 23, Fig. 1*b*, 2*b*, Plate 24, Fig. 3*b*). The cracks at the corners of the mouth were healed. Microscopic examination of a piece of skin taken from the forearm near the site of the biopsy showed, however, that the naked eye had indicated an exaggerated degree of improvement: ' The pigmentation is much less in this specimen than in the previous one ; the hyperkeratosis seems to be of about the same degree, but the zone of hyperkeratosis is more rarified in this specimen, the horny scales being less densely packed. W.W.W.' A blood count showed no appreciable alteration. The patient stated that she felt much better, and her general appearance and sense of well-being seemed improved, but there was no gain in weight, and phases of deep depression still occurred.

Owing to the difficulty of preparing the egg-white concentrate in sufficient quantity, it was now decided to give a full diet, rich in vitamin B_2, with the addition of three teaspoonfuls of marmite daily, and iron in the form of Blaud's pill gr. 20 three times daily. No meat or fish was included in the diet owing to the patient's objection. In the next two weeks there was a gain in strength and weight (5 lb.), and the pigmentation and roughness of the skin ceased to be noticeable except for traces that could be made out if specially looked for. A somewhat paradoxical voracity of appetite, which was said to have been insatiable during the past few years, disappeared, leaving in its stead a more normal appetite readily assuaged by a good meal. The patient was discharged from hospital on the 24th October when the blood count showed erythrocytes 4,000,000, and haemoglobin 52 ; one month later the erythrocytes were 4,600,000 and the haemoglobin 76.

Subsequent progress. In November 1933 a relative wrote : ' Since she left the hospital, although she is physically so enormously improved, and her

whole appearance indeed transformed, yet mentally her condition seems practically unchanged, the depression, indecision, worrying over inessentials, &c. continuing.' One month later, however, a change seems to have occurred; the patient wrote: 'I am feeling very much better, full of more energy and plans for work of all kinds. At last the miracle has occurred— the day seems positively too short for all I want to pack into it.' About this time the dose of iron was reduced, as the patient had the impression that it caused menorrhagia. Subsequent return to more normal menstruation appeared to confirm her view.

In February 1934 the patient was again seen and appeared to be in excellent health. There was still a slight roughness of the skin of the forearm. The next visit of the patient was in September 1934, when she was again in good health, having put on several pounds in weight, and having passed through a hot summer without a return of the skin lesions. Although not seeking sun exposure, she stated that she had not specially avoided the sun except when at its maximum intensity. Her face and forearms were some- what darker in colour than in the winter, but there was no gross hyper- keratosis, although the skin of the forearm was still slightly rough. She now carried out all her daily tasks without tiring, and with goodwill and cheerful- ness. The attacks of melancholia and anxiety had apparently disappeared and the patient stated that she now enjoyed life completely.

Diagnosis of Secondary Pellagra.

The diagnosis of pellagra depends upon the recognition of the characteristic skin lesions. Their nature is indicated in the present case description and in the diagrams; the principal features are summarized by O'Leary: ' The dermatitis which may be in any part of the body, but more frequently on the exposed areas, as hands, forearms, nose, neck, and lower limbs, is characterized by the dull red pigmentation, the desquamation, the demarca- tion or well-defined borders, and the hyperkeratosis which gives the dirty appearance.' The more acute erythema and oedema phase of endemic pellagra is usually less conspicuous and more transitory in secondary pellagra. Pellagrous dermatitis tends to occur more frequently in spring or early summer.

The gastro-intestinal symptoms and signs associated with pellagra are anorexia, nausea, vomiting, diarrhoea with periods of constipation, stomatitis, glossitis, and in the majority of cases, achlorhydria. In secondary pellagra many of these may be absent or inconspicuous.

Mental and neural changes are not necessarily present, but are of diagnostic significance when they occur. Harris (17) states that: ' mental symptoms may come on in any stage of pellagra. . . . they generally appear after the other symptoms have persisted for a time. . . . Psychic phenomena are prominent throughout the course of pellagra, manifesting themselves in the early periods of the disease in vertiginous sensations, loss of memory, mental irritability and melancholy . . . and in later stages by crying and sobbing . . . loathing for food . . . maniacal outbursts.' Spinal cord changes may occur, and usually manifest themselves as subacute combined degeneration.

It is obviously important to recognize the previously existing gastro-intestinal lesion: gastrectomy, gastro-jejunostomy, syphilitic gastritis, alcoholic gastritis, carcinoma of stomach, jejunostomy, duodenal feeding, oesophageal stenosis, stenosis of small intestine, stenosis of large intestine, carcinoma of large intestine, chronic diarrhoea, idiopathic steatorrhoea, ulcerative colitis, and intestinal tuberculosis. The latent period before the development of pellagra may be weeks, months, or years.

The mechanism of the production of secondary pellagra and its etiological significance. If one regards pellagra as a deficiency disease and accepts the view that the missing essential dietary factor is derived from or bound up with protein (Goldberger (16) and others, Chick (10)), it would seem from the list of gastro-intestinal causes (vide supra) of secondary pellagra that the organism might be deprived of this factor in one or more of several ways : the mechanical exclusion of gastric digestion (e.g. gastrectomy, jejunal feeding, a faulty gastro-jejunostomy) ; the absence of some ' intrinsic factor ' normally present in gastric juice (e.g. gastritis) ; the absence of an ' extrinsic factor ' owing to an inadequate diet (e.g. oesophageal stenosis) ; inadequate time for the interaction of ' intrinsic and extrinsic factors ' (e.g. rapidly emptying gastro-jejunostomy) ; inadequate absorption (e.g. diarrhoea) ; destruction of the ' essential factor ' by pathological intestinal flora (e.g. intestinal stenosis).

If one may use the term secondary Addisonian (or megalocytic hyper-chromic) anaemia, it is very striking that the gastro-intestinal precursors (summarized by Wilkinson) of this condition are similar if not identical with those of ' secondary pellagra '. Since Addisonian anaemia is now recognized as a deficiency disease (Castle), the occurrence of 'secondary pellagra' under similar conditions is further evidence in favour of the deficiency theory of pellagra.

Why apparently identical conditions should sometimes produce pellagra, sometimes hyperchromic megalocytic anaemia, sometimes simple microcytic anaemia, sometimes polyneuritis, presumably from deficiency of vitamin B_1 (Minot, Strauss, and Cobb (21)), and most often nothing abnormal is a complex problem that awaits solution.

Are minor manifestations of pellagra frequently missed ?   A diet that would be adequate for a normal person might prove deficient in the presence of a mechanical gastro-intestinal abnormality, e.g. a faulty gastro-jejunostomy. It is in such cases that the occurrence of pain would perhaps determine the habitual use of a diet quantitatively or qualitatively deficient. The irritability and mental depression not infrequently observed in such cases might be manifestations of vitamin deficiency rather than due to alkalosis as is commonly assumed.   An associated dryness and roughness of the skin might also constitute a minor manifestation of pellagra.

Severe dietary restrictions are not uncommon at the present time and are determined by a multiplicity of causes, e.g. poverty, slimming, treatment of disease. The addition of yeast or marmite might be as important a prophy-lactic measure as the giving of cod liver oil to prevent rickets in children.

Is there an association between pellagra and the adrenal gland? In 1902 Finotti and Tedeschi examined the adrenal glands of eight patients dying from pellagra, and found cellular infiltration in five and necrotic changes in three. Symptoms suggestive of Addison's disease (hypotension, pigmentation, subnormal temperature) were described by Rubinato (28) in a male of 58 years of age suffering from pellagra ; at autopsy fibrous atrophy of the adrenal glands was found, and also some atrophy of the anterior lobe of the pituitary gland chiefly affecting the chromophobe cells. In his monograph on pellagra (1929) Harris stated that it had been observed by many writers that pellagrous patients occasionally developed a typical form of Addison's disease with pathological changes in the adrenals. More recently Thannhauser (32) remarked upon a possible connexion between pellagra and endocrine disorders ; he described a male of 41 who appeared to be suffering from chronic Addison's disease and suddenly developed pellagra ; at the autopsy of this patient Aschoff found atrophy of the zona glomerulosa of the adrenal cortex with disappearance of lipoid, and a very small hypophysis with reduction of basophil cells.

The patient with pellagra described in this article was sent to the writer as a possible case of Addison's disease, and this diagnosis was apparently suggested by areas of pigmentation distinct from the typical pellagra lesions. Finotti and Tedeschi (14) took the view that increased pigmentation in itself was not an essential part of pellagra, but that in many cases there is no border line between Addison's disease and pellagra. By the courtesy of Dr. C. S. Roach-smith, the writer was invited to see a patient with pellagra under his care at the Napsbury Mental Hospital. The patient was a woman of 31 suffering from an anxiety depressive state over a period of twelve years, with remissions. On 23rd September 1933 she was admitted in a relapse phase with a history of some weeks' diarrhoea, and at the time of admission it was noted that her skin was of dark colour. She was a little difficult with her food, but with persuasion appeared to be taking an adequate diet, including milk and eggs. On 19th October, quite suddenly, there appeared typical pellagra lesions with hyperkeratosis and demarcation on the wrists (section 5) and thumbs. She was seen by the writer on 27th October, when her blood-pressure was 80 mm. of mercury systolic, and 50 diastolic ; the pigmentation was diffuse and characteristic of Addison's disease, being especially marked over pressure points and including a small patch on the mucous membrane of the left cheek. Eucortone, 5 to 10 c.c., was injected daily for twenty-five days and marmite and yeast were added to the diet. The pellagra lesion disappeared within a few weeks, and the diarrhoea had ceased and the pigmentation almost disappeared by the end of November. The blood-pressure rose to 104 mm. Hg. systolic and 80 diastolic on the 29th November, but during the next few months tended to fall to lower levels intermittently. The patient, however, recovered in strength and well being and was able to leave her bed in February 1934. In May she developed a fatal broncho-pneumonia and at autopsy no gross lesion was then present in the adrenal glands.

Experimental work on animals throws some light on the relationship between pellagra and the adrenals. In 1915 Rondoni and Mantagni (quoted by Harris) produced pellagra by feeding animals on a maize diet, and observed at autopsy degenerative changes in the adrenal cortex. Findlay (13) observed hypertrophy and congestion of the adrenals of rats fed on a vitamin B_2 deficiency diet and showing the skin lesions of experimental ' rat pellagra '. Lockwood and Hartman (20) recorded hypertrophy of guinea-pig adrenals in vitamin C and B_1 deficiencies, and atrophy in vitamin A deficiency ; injections of cortical extract delayed the onset of symptoms in avitaminosis C and B_1.

Packard and Wechsler (24) report four patients suffering from chronic malnutrition and showing signs and symptoms of adrenal insufficiency. At necropsy ' the suprarenal lesion was one of hypertrophy and degeneration. The latter change was evidenced by vacuolar degeneration of the cortical cells, with areas of necrosis and regeneration, and hyperaemia, oedema, haemorrhages, and capillary and venous thromboses of the interstitial tissue.'

It would appear from the evidence that (1) a vitamin deficiency might produce both pellagra and adrenal insufficiency in the same patient ; (2) that adrenal insufficiency might occur in the course of pellagra as a sequel to the associated absolute or conditioned malnutrition ; (3) that pellagra might occur in the course of chronic Addison's disease as a sequel to the associated anorexia.

Summary

1. A case of pellagra following gastrectomy, and apparently cured by vitamin B_2, is described.

2. The diagnosis of secondary pellagra is discussed and the necessity for observing and preventing minor manifestations is stressed.

3. The mechanism of the production of secondary pellagra is described and its etiological significance indicated.

4. A relationship between pellagra and adrenal hypo-function is found to exist.

REFERENCES

1. Aschoff, L., *Münch. med. Wchnschr.*, 1933, lxxx. 296.
2. Barnes, J. M., *Ann. Clin. Med.*, Balt., 1926, iv. 552.
3. Bender, W. L., *Journ. Amer. Med. Assoc.*, Chicago, 1925, lxxxiv. 1250.
4. Bennett, T. S., Hunter, D., and Vaughan, J. M., *Quart. Journ. Med.*, Oxford, 1932, xxv. 603.

5. Biggam, A. G., and Ghallionni, P., *Lancet*, Lond., 1933, ii. 1198.
6. Bigland, A. D., *ibid.*, 1923, ii. 1295.
7. Bryan, R. C., *Virginia Med. Monthly*, Richmond, 1919, xlvi. 107.
8. Castle, W. B., Heath, C. W., Strauss, M. B., and Townsend, W. C., *Journ. Amer. Med. Assoc.*, Chicago, 1931, xcvii. 904.
9. Chick, H., *Lancet*, Lond., 1933, ii. 341.
10. Chick, H., *Proc. Roy. Soc. Med.*, Lond., 1934, xxvii. 473.
11. Ellis, R. W. B., *Amer. Journ. Dis. Child.*, Chicago, 1930, lxxxv. 1036.
12. Eusterman, G. B., and O'Leary, P. A., *Arch. Int. Med.*, Chicago, 1931, xlvii. 633.
13. Findlay, G. M., *Journ. Path. and Bact.*, Edinb., 1928, xxxi. 353.
14. Finotti and Tedeschi (quoted by Harris).
15. Goldberger, J., Waring, C. H., and Tanner, W. F., *U. S. Pub. Health Rep.*, Wash., 1923, xxxviii. 2361.
16. Goldberger, J., and Wheeler, G. A., *ibid.*, 1927, xlii. 1299 and 2383.
17. Harris, H. F., *Monograph on Pellagra*, N. York, 1919.
18. Hutchison, R., and Patterson, D., *Brit. Med. Journ.*, Lond., 1923, ii. 647.
19. Levy Simpson, S., *Proc. Roy. Soc. Med.*, Lond., 1934, xxvii. 484.
20. Lockwood, J. E., and Hartman, F. A., *Endocrinology*, Los Angeles, 1933, xvii. 501.
21. Minot, G. R., Strauss, M. B., and Cobb, S., *New England Journ. Med.*, Bost., 1933, ccviii. 1244.
22. Morawitz, P., and Mancke, R., *Arch. f. Verdauungskr.*, Berl., 1934, lv. 3.
23. O'Leary, P. A., *Med. Clin. N. Amer.*, Philad., 1926, x. 647.
24. Packard, M., and Wechsler, H. F., *Arch. Int. Med.*, Chicago, 1934, liv. 18.
25. Rolph, F. W., *Can. Med. Assoc.*, Toronto, 1916, vi. 123.
26. Rondoni and Mantagni (quoted by Harris).
27. Rowlands, R. A., and Levy Simpson, S., *Lancet*, Lond., 1932, ii. 1202.
28. Rubinato (quoted by Harris).
29. Spies, T. D., and DeWolf, H. F., *Amer. Journ. Med. Sci.*, Philad., 1933, clxxxvi. 521.
30. Stannus, H. S., and Gibson, C. R., *Quart. Journ. Med.*, Oxford, 1934, xxvii. 211.
31. Straus, M. B., *Journ. Amer. Med. Assoc.*, Chicago, 1934, ciii. 1.
32. Thannhauser, S. J., *Münch. med. Wchnschr.*, 1933, lxxx. 291.
33. Thaysen, T. E. H., *Acta Med. Scand.*, Stockholm, 1932, lxxviii. 531.
34. Thaysen, T. E. H., *Monograph on Non-tropical Sprue*, Copenhagen and Lond., 1932.
35. Turner, R. H., *Amer. Journ. Trop. Med.*, 1929, ix. 129.
36. Ungley, C. C., *Lancet*, Lond., 1932, ii. 1426.
37. Wilkinson, J. F., *Quart. Journ. Med.*, Oxford, 1933, xxvi. 281.
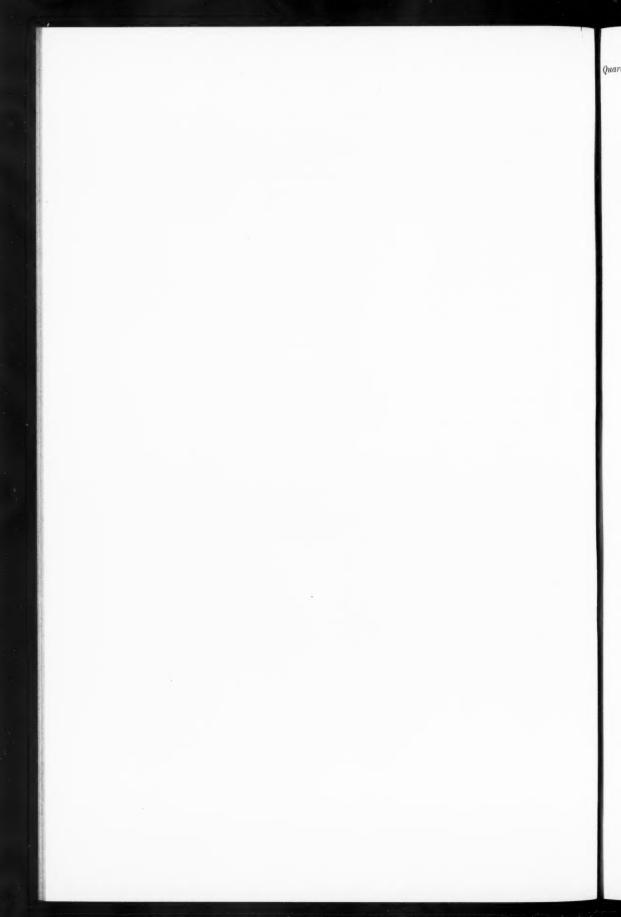
FIG. 1 *a*. On admission

FIG. 1 *b*. After treatment with vitamin B$_2$

FIG. 2 *a*. On admission

FIG. 2 *b*. After treatment with vitamin B$_2$
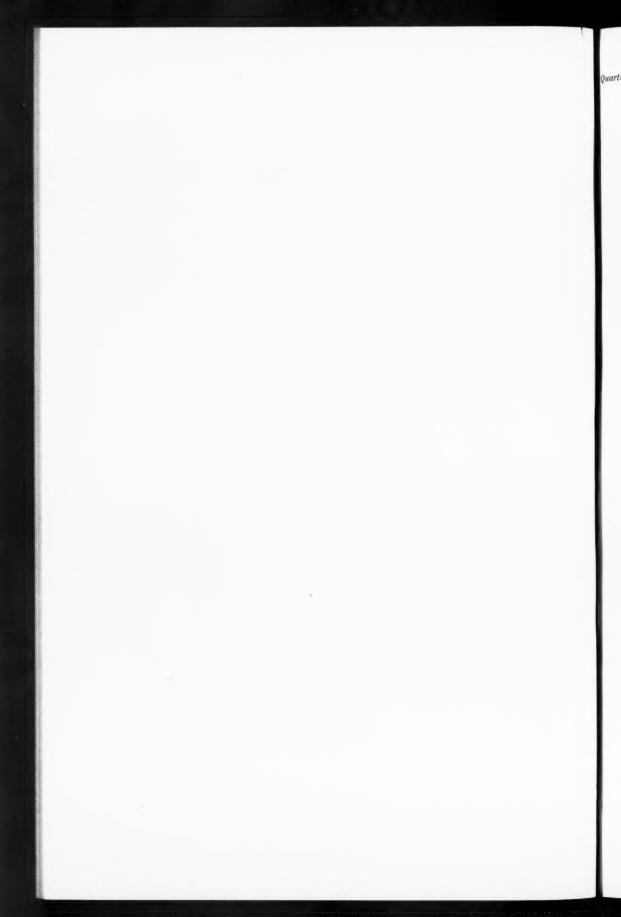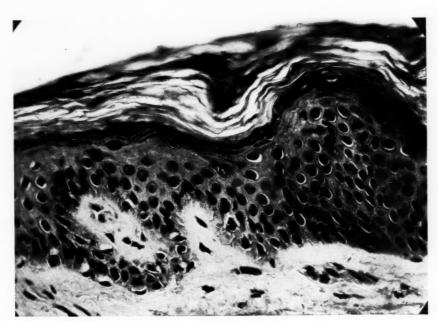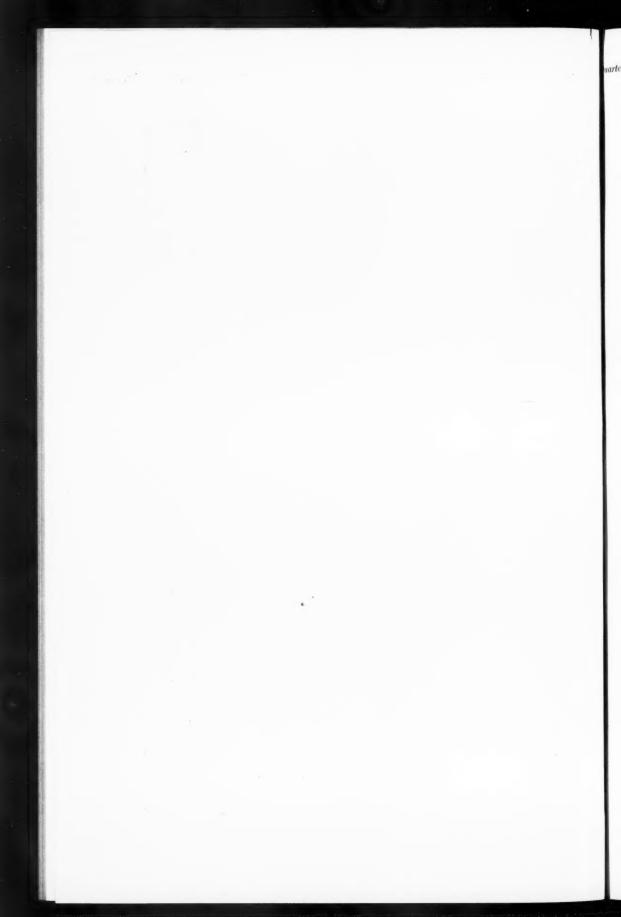
FIG. 3 a. On admission   FIG. 3 b. After treatment with vitamin B₂

FIG. 4. 'Secondary pellagra.' Section of skin of forearm showing hyperkeratosis and pigmentation of basal layer of epidermis
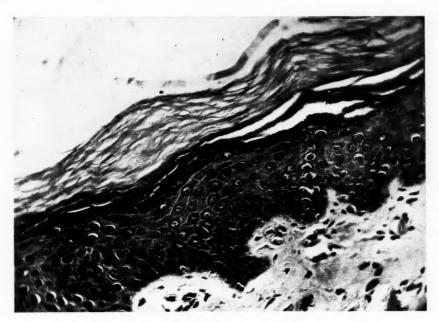
Fig. 5. 'Asylum pellagra.' Section of skin of wrist showing hyperkeratosis
and pigmentation of basal layer of epidermis
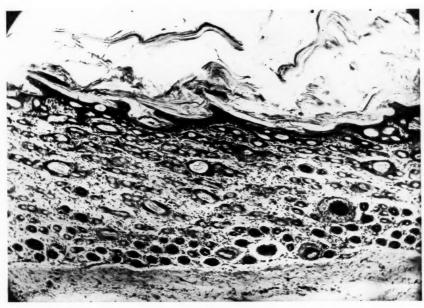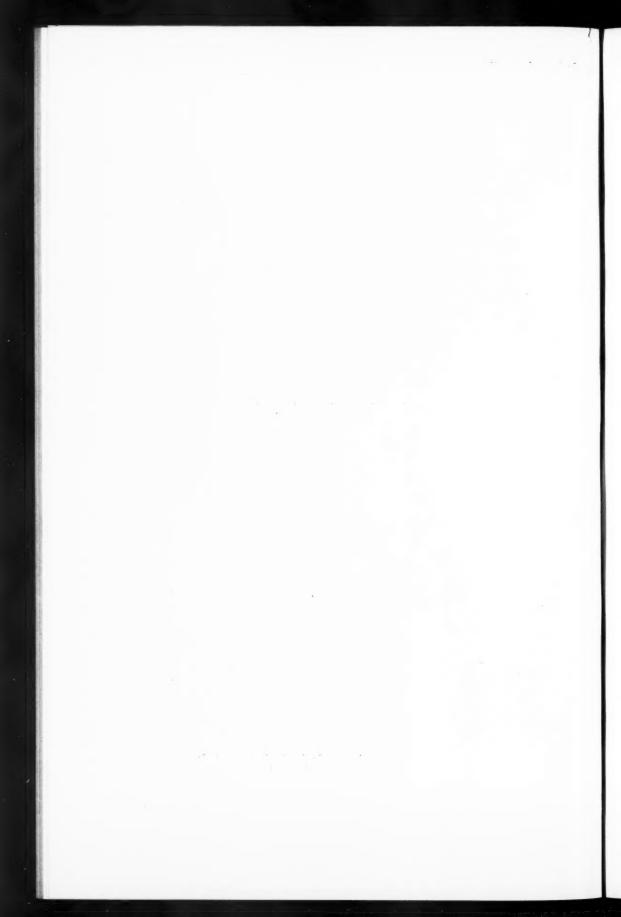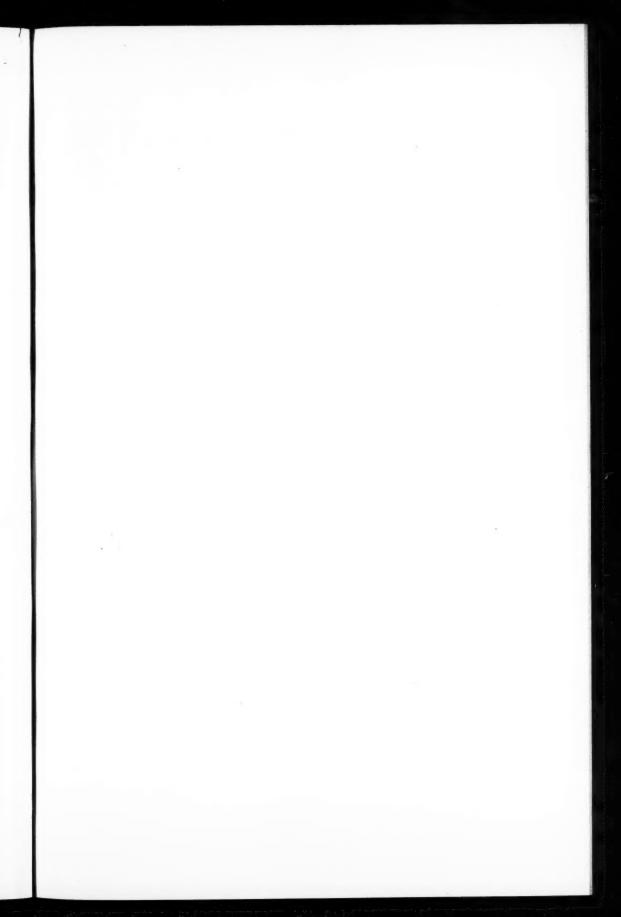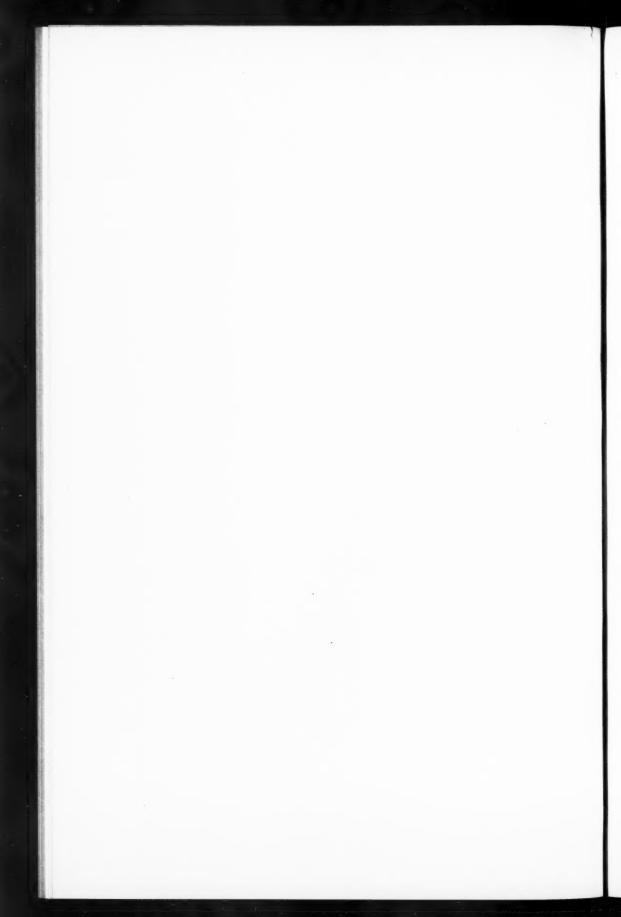
Fig. 6. 'Rat pellagra.' Section of skin showing hyperkeratosis
and cellular infiltration of dermis

(By courtesy of Miss H. Chick and Professor J. C. G. Ledingham)

TUBERCULIN ALLERGY IN ACUTE INFECTIOUS DISEASES:

A STUDY OF THE INTRACUTANEOUS TEST [1]

By J. S. WESTWATER

With Plate 26

Introduction

THE intracutaneous tuberculin test is rapidly displacing the original scarification method of von Pirquet in clinical work, and, as it seems likely to become the standard method, it is necessary that any possible fallacies should be determined. One such is the effect of the acute infectious diseases on tuberculin allergy; it is known that certain exanthemata, particularly measles, can temporarily suppress the response to the von Pirquet test. In other acute infections similar effects have been claimed and disputed in turn. In any such investigation the possible duration of a temporary suppression of the tuberculin response would be important, especially in regard to the value of the negative result in the diagnosis of tubercle infection in childhood. In most studies on the subject this latter point has received little attention.

At the Park Hospital, London, during the period 1931–3, some 2,000 cases of the acute infectious diseases were studied, including measles, scarlet fever, chicken-pox, diphtheria, and whooping-cough. The method adopted was to perform intradermal tests on admission and thereafter at intervals varying in each disease until the patient left hospital. It was considered better to test a large number of cases relatively infrequently rather than a few intensively, as repeated tuberculin tests at short intervals are known to stimulate allergy and this would tend to minimize any possible depressing effect of the acute infection.

Technique. For this investigation the Mantoux test was used according to the usual technique of injecting 0·1 c.c. of tuberculin intradermally. As it was proposed to record the reactions quantitatively, constant accurate dosage was necessary, and this was facilitated by using a Vim 1 c.c. tuberculin syringe, which is graduated to 0·01 c.c.

Koch's Old Tuberculin was used, dilutions being made from the standardized preparation of Burroughs, Wellcome, & Co. Although it is generally considered that the allergic subject will react to either human or bovine tuberculin, dilutions were prepared from equal parts of human and bovine O.T. to

[1] Received August 1, 1934.

obviate any possible fallacy of this nature. The dilution of 1 : 1,000 was used throughout, except for a certain number of measles cases in which a 1 : 100 dilution was used. The diluent commonly adopted is 0·5 per cent. carbol-saline, but the carbolic acid tends to make the protein unstable. To avoid this, the special toxin diluent described by Glenny and others (1928) for the Schick and Dick tests was used. Dilutions were made up fresh every three weeks, as the tuberculin deteriorates slightly even when using the special toxin diluent referred to above.

Assessment of sensitivity. In order to obtain a measure of a patient's tuberculin sensitivity, the reactions were recorded according to the degree and size of response, as follows :

(a) *Size.* The size of the reaction was indicated by estimating the mean diameter in millimetres. With 0·1 c.c. I have found that it varies from 5 mm. to 20 mm. It is rare in children for reactions to exceed 20 mm. in diameter. Generally the area of reaction is larger in the more intense reactions up to the limit of 20 mm. At the same time the age factor minimizes the value of accepting size absolutely. In younger children one cannot raise a wheal of the same size with 0·1 c.c. as in the older child. This probably accounts for Dickey's (1929) observation that the average size of the Mantoux reaction increases up to the sixth year. I have found that the average size increases up to the third year. Accordingly, in children one has to depend more on the degree than on the size of response in comparative work.

(b) *Degree.* The character of the reaction was graded into six categories as follows :

1. (+) a simple erythema with no infiltration, only to be accepted as positive if it persists at least forty-eight hours; it is best confirmed by a second test.

2. + a mild reaction showing an area of infiltration of the skin, pink or red in colour, but sometimes barely tinted. It is a raised area of erythema—a maculo-papule.

3. + + a moderate reaction showing a yellowish oedema in the centre of the red infiltrated area.

4. + + + a more intense response in which the raised infiltrated area is wholly oedematous.

5. + + + + a marked reaction with actual vesiculation, often with haemorrhage into the little vesicles.

6. + + + + + the most severe of all, in which superficial necrosis follows on the vesiculation, a dry slough separating in one or two weeks : such a severe reaction is rare with a 1 : 1,000 dilution.

Surrounding the more intense reactions there may be a halo of pink erythema ; this erythema does not last more than forty-eight hours. It has been indicated by measuring the breadth in millimetres; thus ' E. 15 ' means a surrounding zone of erythema 15 mm. broad.

Unless otherwise stated, the term ' Mantoux test ' refers to the 1 : 1,000 dilution. Thus 'Mantoux test + + + 20 mm.' indicates a response showing a raised infiltrated area of 20 mm. in diameter wholly oedematous ; ' +15 mm.' a raised infiltrated macule of 15 mm. diameter without oedema. By assessing the reactions to a given dilution in this way, some quantitative record of the individual's tuberculin sensitivity was obtained.

Measles

In 1907 Preisich, using the von Pirquet test, first observed that the skin response to tuberculin was lost temporarily in measles.   Von Pirquet himself a year later published his own observations; he found the reaction was suppressed in the four days following the appearance of the measles rash, and to this phenomenon he applied the term 'anergy'.   Various others using the scarification test have obtained similar results—notably Teissier and Léon-Kindberg (1911), Moltschanoff (1912), Lesné and Coffin (1926), Debré and Papp (1926), and Lereboullet and Baize (1931).   But whereas von Pirquet found that all cases lost their reaction, subsequent studies show that the reaction can persist in the milder attacks such as those modified by convalescent serum.   Von Pirquet's original term 'anergy', implying complete lack or loss of sensitivity, is therefore not strictly applicable to the phenomenon.   Such a term as 'hypo-sensitivity' would be more suitable.

With the intradermal method Mantoux and Harvier (1910) recorded that in thirty-two subjects known to be sensitive to tuberculin, the reaction was lost during measles.   Mitchell and his co-workers (1929), also using the Mantoux test, found that in 200 cases there was an increase in the percentage of positive reactors from 3·5 per cent. in the acute stage to 15 per cent. in convalescence, indicating that a proportion of the allergic subjects failed to react in the eruptive period.   They did not attempt to define the duration of the period of hypo-sensitivity.

Von Pirquet performed tests daily; this frequent repetition of the tests might tend to stimulate allergy and cause a positive response to return sooner, and analysing his cases one finds that positive reactions returned earlier in those on whom daily tests were begun in the incubation period than in those in which the tests were not started until the prodromal or eruptive phase.   To avoid such a fallacy in the present investigation, cases were tested relatively infrequently—usually at weekly intervals—the initial test being done as a rule the day after admission to hospital when the rash was at its height.

Observations in 900 cases of measles.   With few exceptions, the cases came under observation in the acute stage of measles, with their reaction to tuberculin not known.   In these circumstances, any effect of the acute infection on tuberculin sensitivity could only be demonstrated by performing tests both in the acute and later periods of the disease and noting whether patients, negative in the eruptive period, gave positive reactions to subsequent tests.   The method adopted was to test patients the day after admission, when the rash or its staining was still present, and subsequently at intervals of a week to a fortnight to cover varying periods of convalescence.   In this way most patients had only two or three tests done, thus minimizing any stimulating effect of the tuberculin injected. The results have been tabulated according to whether tests were done in the first week of the disease—the eruptive period—or later.   Included in

the table, but in a separate category, are the results in those cases on whom only one tuberculin test was done.

TABLE I

Period of test.	Results from tests repeated on same group of cases.		Results from single tests on different groups of cases.		Total.
	1st week.	2nd week or later.	1st week.	2nd week or later.	
Number tested	602	602	112	186	900
Number positive	21	38	8	4	50
Per cent. positive	3%	6%	7%	2%	5%

From the above table, it will be seen that the Mantoux test was applied to 602 cases, both in the eruptive period and later. Altogether, thirty-eight of these reacted to the test, but only twenty-one gave a positive result in the first week. This means that there were seventeen cases subsequently proved tuberculin-sensitive, who failed to respond to the initial test in the acute stage, and suggests that measles can suppress the reaction to 1 : 1,000 O.T. In this series it occurred in seventeen out of thirty-eight cases—or approximately 45 per cent.

As the patients were discharged from hospital at different times in convalescence, it follows that, in the 602 cases submitted to the Mantoux test both in the eruptive phase and at subsequent intervals in convalescence, the period between the initial and final tests will vary. The results are classified in the following table to show the periods covered by the repeated tests.

TABLE II

	Period between initial and final tuberculin tests.			Total.
	1st–2nd week.	1st–3rd week.	1st–4th week.	
No. of cases	234	180	188	602

The table shows that in 234 cases tuberculin tests were done both in the first week and the second; in another group of 180 cases, they were continued into the third week, while in 188 the final tests were done in the fourth week.

The negative results in the cases previously or subsequently proved tuberculin-sensitive, if classified according to the period of the disease, will give some indication of the length of time during which the response to the Mantoux test in 1 : 1,000 dilution may be suppressed following the onset of measles. In this next table such negative tests are grouped according to the week of the disease in which they were obtained.

TABLE III

Incidence of Negative Tests in Allergic Subjects

Period of disease	1st week	2nd week	3rd week	Total.
Negative results in allergic cases	15	2	0	17

In these allergic subjects the majority of the negative reactions occurred in

the first week, but in two cases negative results were obtained in the second week. No negative reactions occurred after the second week. This would suggest that the Mantoux reaction in 1 : 1,000 dilution is commonly suppressed in the first week, and on occasion also in the second week.

Longer periods than this have been reported by workers using the von Pirquet test. Klein (1923) and Kollar (1926) obtained negative reactions in the third week, while Nobécourt and Liège (1930) have reported two cases negative as late as the twenty-fifth and thirtieth days. Cases persisting negative as long as two to four months after measles have been observed by Lereboullet and Baize (1931) and Debré and Papp (1926).

In this present investigation 128 cases, negative to the Mantoux test while in hospital, i.e. within a month of the onset of their illness, were re-tested two to four months afterwards. Only one case gave a positive result. That occurred four months after the attack of measles : the last negative reaction, obtained while this patient was in hospital, was on the tenth day of the disease. Assuming that this case had not actually acquired a sensitivity to tuberculin in the interval of four months, then it may be considered that the reaction had been suppressed till the tenth day, and was regained some time in the interval between the tenth day and the fourth month. This may be taken to corroborate the results already given, namely, that the Mantoux reaction may be suppressed at least as late as the second week.

The other 127 cases were all negative to the late tests done two to four months after their attack, thus confirming the results already obtained while the patients were in hospital. These observations, therefore, do not indicate that the Mantoux reaction may be suppressed beyond the tenth day of measles.

In the patients on whom only one test was done, the results given in Table I are conflicting : 7 per cent. were found positive in the first week, while a series of comparable age grouping, tested in the second week or later, showed 2 per cent. positive. These results would not suggest any effect from the acute infection, but apart from the series of cases being small, there is a deliberate error in sampling, in that an endeavour was always made to re-test any case negative in the acute period, whereas re-tests were avoided in patients who gave frank positive results initially, lest severe reactions be obtained to subsequent tests. This policy must necessarily have increased the proportion of positive to negative reactors in the single tests performed in the first week, and can explain the anomalous results. The same error applies to the tables of single tests which will be quoted for the other diseases considered.

The mechanism of temporary hypo-sensitivity. In the following table it is to be noted that the results of all tests done on the allergic subjects during the first eleven days are included. The five ' late ' positive reactions are those in which a latent interval of two days or more elapsed before a positive response appeared.

TABLE IV

Results of Mantoux Tests in Tuberculin-sensitive *Subjects during Measles*

Day of rash	1	2	3	4	5	6	7	8	9	10	11
Positive reactions	2	6	2	2	4	4	2	2	1	2	2
'Late' positive reactions	—	1	3	1	—	—	—	—	—	—	—
Negative reactions	3	2	6	4	4	1	—	—	—	2	—

The table shows that positive results were obtained at all stages, illustrating the fact that the effect on the reaction to 1 : 1,000 O.T. is not absolute, even in the most acute phases. It will be seen that the negative results were most common in the first five days. This is similar to von Pirquet's original observations with the scarification test. The latest day that negative reactions occurred was the tenth day. It is possible, therefore, for a Mantoux reaction to be suppressed for as long as ten days from the onset of a measles rash.

Considering this table from the point of view of the effect of the rash itself on the depression of sensitivity, it will be seen that in the first two days of the rash fourteen Mantoux tests were done on allergic subjects: there were eight positive reactions obtained against five negative, whereas, combining the results on the third and fourth days, there were only four positive reactions against ten negative. Later, on the fifth and sixth days, there were more positive than negative results, viz. eight to five. It is apparent, therefore, that the negative reactions were most frequent on the third and fourth days. This is the period when the rash is fully established, if not just beginning to wane. Analysed in this way these results suggest that the maximum effect on sensitivity follows upon the full development of the rash.

Results in cases whose tuberculin-sensitivity was already known. A more exact measure of any depressing influence would be obtained by a study of cases whose reaction to tuberculin was already known prior to the onset of measles. In the whole series observed, there were six children who were already known to be sensitive to tuberculin, and whose reaction to the Mantoux test had been recorded according to the standards set out at the beginning of this paper. In those cases more frequent tests were done during the attack of measles. The results are set out in the table on p. 209. In the second column is given the reaction to 1 : 1,000 O.T. prior to the onset of measles. In the subsequent columns are given the results of tests performed during the attack of measles, recorded according to the day of the true rash. 'T' signifies that a tuberculin test was done on the day of the rash indicated at the head of the particular column in which it stands. Reading to the right on the same line are the reactions, if any, obtained on subsequent days, measured, for simplicity, by degree only. For example, in Case 19 a test was done the day before the rash appeared, and the next day, the first day of the rash, there was a response of '(+)', i.e. an erythema only, which persisted till the third day; there was no response on the fourth, fifth, and sixth days, but on the seventh an erythema reappeared. In the same case another test was done on the second day of the rash with no

subsequent reaction, while a third test on the fourth day gave a '(+)' reaction.

TABLE V
Mantoux reaction.

Case.	Prior to measles.	During measles. Day of rash.							
		0	1	2	3	4	5	6	7
19*	++	T	(+)	(+)	(+)	—	—	—	(+)
				T	—	T	(+)	(+)	(+)
17	+			T	—	(+)	(+)	+	(+)
					T	—	+	+	(+)
25	+			T	+	—	—	—	+
							T	+	++
49	+++	T	+	+	+	(+)			
				T	(+)	(+)	(+)		
						T	+++	+++	+++
30	++			T	+	+	+		
						T	++	++	+
18	+			T	—	—	—	—	—
					T				

* Tests *during* measles in this case were made with 1 : 10,000 dilution of O.T.

The table shows that there is a depression of sensitivity with the onset of measles. If the reaction to 1 : 1,000 O.T. was not completely suppressed, the degree of response obtained was much less than that obtained prior to the onset of the disease.

This table also throws some light on the mechanism of this effect. For instance, in Case 19 a tuberculin test was done the day before the rash appeared, and next day gave a response of ' (+)' along with the appearance of the rash : a subsequent test was done when the rash had been out forty-eight hours with a negative result. This was the period when the rash was at its height. A similar effect is seen in Case 49 : a test done the day before the rash appeared gave a ' + ' response, while a test on the second day of the rash gave only a '(+)' response (erythema), although the earlier test still showed a ' + ' reaction (erythema with infiltration). These results, therefore, suggest that the depression of tuberculin sensitivity is related to the development of the true measles rash, and that the maximum effect is correlated to the height of the eruption.

Another feature is the occurrence of unduly delayed or 'late' reactions. For instance, in Case 17 a test on the first day of the rash did not show a positive response till the fourth day, i.e. not until the height of the eruption had passed. The reaction itself was not at its maximum until the sixth day, five days after the test was done. Unduly delayed reactions occur occasionally in apparently normal subjects, but in measles they occurred relatively frequently. Reference to Table IV shows that five 'late' reactions were observed, and they occurred in the period of the eruption—the maximum number (three) being on the third day, which appears to be the time of maximum hypo-sensitivity.

Allied to these 'late' reactions is the phenomenon of reactivation of a positive response already faded. Referring to Table V, it will be seen that in Case 25 a test done on the first day of the rash gave a ' + ' response on the second day, but was negative thereafter until it reappeared on the seventh day. The same phenomenon also occurred in Case 19; the test done the day before the rash appeared was reactivated after being negative for three days. This reappearance of the reaction seems to be due to the stimulation of the subsequent tests, but reactivation did not occur till the seventh day in each case. It is possible that the depressing effect of the exanthem was persisting until the sixth day.

Whatever may be the cause of those unduly delayed or 'late' positive reactions, as they occur at times in tuberculin-sensitive subjects without intercurrent infections, in measles at any rate they occur relatively frequently and appear to be related to the temporary depression of sensitivity. It may be that the tuberculin injected into the skin remains at the site of the test long enough to evoke the characteristic response when the cells have recovered from their reaction to the measles virus.

If the temporary depression of sensitivity be due to the rash, some relation might be expected between the intensity of the eruption and the incidence of negative results in allergic subjects. In the following table the tuberculin-sensitive cases have been divided into two categories—those with a mild rash and those with a moderate or severe rash—the basis of the classification being the day on which the rash began to fade, whether it was the second day or later. The results obtained from tests made during the first five days of the disease, classified in this way, show that with the more intense rashes there is a greater proportion of negative results.

TABLE VI

Reaction in 1st week of measles.	Type of rash.	
	Mild.	Severe.
Positive reactions	9	9
'Late' positive reactions	1	4
Negative reactions	6	13

This table shows that the more intense the rash, the greater proportion of negative results obtained. In the group with a mild rash, there were six negative to nine positive reactions, whereas in the group with a severe rash there were thirteen negative to nine positive reactions.

Another factor is the degree of sensitivity of the individual patient, which can be gauged by the response obtained to a tuberculin test in convalescence. For this purpose the cases have been classified into two groups—those with a reaction of ' + + ' or less and those with a reaction of ' + + + ' or more, as measured by tests made in the convalescent period. The positive, delayed, and negative results have been tabulated in each class, but including only those reactions obtained during the period of maximum hypo-sensitivity, i.e. the first week.

TABLE VII

Reaction in 1st week of measles	Degree of allergy.	
	+ + or less.	+ + + or more.
Positive reactions	6	11
'Late' positive reactions	2	3
Negative reactions	9	7

Table VII shows that in the less allergic group there were six positive to nine negative reactions, while in the more sensitive cases there were eleven positive to seven negative reactions. Therefore, with the higher degree of sensitivity, there is a greater proportion of positive reactions. This is irrespective of the type of rash. Accordingly, there seem to be two opposing factors influencing the result to a tuberculin test in measles, viz. sensitivity and the rash. The more intense the rash, the more likely is the result to be negative, while the more allergic the subject, the greater is the chance of a positive response.

If the depression of sensitivity be due to the action of the rash, its presence or absence at the actual site of the test might be expected to show some relation to the subsequent tuberculin response. In this study, the volar aspect of the forearm was the site chosen for the Mantoux tests in all the children with the exception of one case (No. 19) in which the tests during the eruptive period were done on the abdomen. The measles rash as a rule appears first on the face and neck, quickly spreading to the trunk and finally to the limbs. It usually appears on the forearm on the second or third day, but often quite profusely in the first twenty-four hours. In mild cases the rash may abort early, with only a few isolated lesions having appeared on the forearms.

When performing tests on those patients in whom the measles rash was actually present, a note was made as to whether or not there were macules present at the site of injection. The observations were confined to the first three days, as, by the fourth day, the eruption is beginning to fade even in the severe types. The results of such tests in twenty-one allergic cases are given below classified according to whether a positive or negative reaction was obtained.

TABLE VIII

Rash.	Mantoux reaction.	
	Positive.	Negative.
Present at actual site of test	3	5
Absent at actual site of test	7	6

This table shows that with the rash present at the actual site of the test, three positive to five negative reactions were obtained, whereas in the absence of the rash, there were seven positive to six negative reactions, i.e. there was a slightly greater proportion of negative results when the rash was present at the site of injection. The series of cases is small and the difference in the proportions hardly sufficient to be regarded as significant,

but taken in conjunction with the observations already given, it is at least suggestive that the depression of the tuberculin response may be related to the local effect of the rash.

One case, No. 19, is of particular interest. This was a girl of 6 years, known to be sensitive to tuberculin, and who had two Mantoux tests done prior to the onset of measles. A summary of the case is as follows:

9/2/32. Mantoux test performed on *right* arm – pos. + 17 mm. (twelve days prior to onset of measles).

16/2/32. Mantoux test performed on *left* arm – pos. + + 20 mm. (five days prior to onset of measles).

21/2/32. Prodromal stage of *measles* recognized by onset of fever and the presence of Köplik's spots: no catarrh or rash present.

On this date it was noted that a bright red erythema had appeared on the right arm at the site of the tuberculin test done twelve days before. One could not say whether this was a reactivation of the tuberculin reaction or actually an early localization of the measles rash.

22/2/32. A typical morbilliform rash appeared on the face, neck, and trunk.

Fig. 1, Plate 26, shows the appearance of both arms on this date. It will be seen that on the right arm what had been, twenty-four hours previously, simply an erythema at the site of the old tuberculin reaction was now a definite localization of the measles rash itself. The central area was typically the dark red, rather irregular maculo-papular eruption of measles: it did not resemble a tuberculin reaction. Surrounding the central area can be seen smaller scattered morbilliform lesions.

It would appear, therefore, that the tuberculin test, done twelve days before, had left the skin of this area in a hyper-sensitive state, such that on the first day of the measles rash, when it was just appearing on the head and trunk, there was also this early localization on the forearm.

On the left arm there was also a localization of the eruption, but only at the periphery of the site of the tuberculin test done five days before. Actually in the centre was the dark purple stain of the tuberculin reaction unaffected by the rash; round it there was a zone, appearing as a halo, in which there was rather faint, small morbilliform macules, and beyond that again a localization of bright discrete maculo-papules, comparable to those appearing on the right arm.

On the left arm it would seem that the cells of the skin at the actual site of the tuberculin reaction were still in a refractory state and therefore did not respond to the measles virus. Immediately round that, in the halo zone, the cells were just recovering, while the cells at the periphery, receiving the minimal effect from the tuberculin, had recovered sufficiently to reach a hypersensitive condition, comparable to that of the cells at the site of the older reaction on the right arm.

This same case illustrates the relation of the rash to the tuberculin response in the converse way. On Fig. 2, Plate 26, is seen the appearance

of the abdomen on the first day of the measles rash. Below, and to the right of the umbilicus, is a positive response to a Mantoux test done twenty-four hours before, when the rash had not yet appeared. This shows that the tuberculin, having reached the skin before the rash actually appeared, evoked a characteristic response.

Fig. 3, Plate 26, shows the appearance of the abdomen eight days later— the ninth day of the rash. The stain of the first test is still visible. To the left of the umbilicus no stains are visible, although two tests were performed there, one on the second day of the rash and one on the fourth. Both these tests were negative. The tuberculin on each occasion was injected into areas of skin already reacting to the measles virus. Above, and to the right of the umbilicus, can be seen the response to a tuberculin test done on the seventh day, when the skin was recovering from its reaction to the acute infection.

These observations, therefore, would seem to indicate that it may be a similar mechanism which reacts to both factors—the virus of infection or the tuberculin. While reacting to one it is apparently refractory to the other.

The use of the Mantoux test with 1 : 100 dilution of O.T. In ordinary clinical work, 1 : 1,000 is the usual dilution of O.T. used for the Mantoux test, and for that reason was adopted for this investigation. The results already given, however, demonstrate that although there is a depressing effect on sensitivity, there is not a complete suppression of the reaction; it varies according to the character of the rash and the patient's sensitivity. If this effect be not absolute, it is possible that by using a stronger solution of tuberculin for the test, the effect of the exanthem might be counter-acted.

In a small series of cases a 1 : 100 dilution was used as well as 1 : 1,000. In one group an initial test was done with a 1 : 1,000 dilution, and in the second week another 1 : 1,000 test performed, followed in forty-eight hours, if negative, by a 1 : 100 test; in a certain number a further 1 : 100 test was done in the third week. In the other group the initial test was made with the 1 : 100 dilution, and subsequent tests carried out as in the first group— a 1 : 1,000 test followed by a 1 : 100 test in forty-eight hours.

TABLE IXA

Reaction in 1st week.		Reaction in 2nd week.				Reaction in 3rd week.	
1 : 1,000 O.T.		*1 : 1,000 O.T.*		*1 : 100 O.T.*		*1 : 100 O.T.*	
Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.
26	—	26	—	25	1	—	—
26	—	26	—	26	—	26	—

In the above table are the results in fifty-two cases in which the initial test was done with 1 : 1,000 O.T. In the twenty-six patients who were tested in the acute stage and the second week, there was one case which reacted positive to a 1 : 100 dilution forty-eight hours after a negative

response to 1 : 1,000. As the effect of the exanthem can last into the second week, one cannot conclude that the 1 : 100 test revealed a positive reactor that would otherwise have been undetected, because it is possible that sensitivity was being recovered in the interval of two days between the 1 : 1,000 and the 1 : 100 tests.

In the other twenty-six cases a 1 : 100 test was done in the third week, as well as in the second, but no positive results were obtained.

TABLE IXʙ

Reaction in 1st week.		Reaction in 2nd week.				Reaction in 3rd week.			
1 : 100 O.T.		*1 : 1,000 O.T.*		*1 :100 O.T.*		*1 : 1,000 O.T.*		*1 : 100 O.T.*	
Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.
38	—	36	2	36	—				
25	—	—	—	—	—	25	—	25	—

In this table the test in the acute phase was made with the 1 : 100 dilution and the subsequent tests as before, i.e. 1 : 1,000 followed in forty eight hours by 1 : 100. It will be seen that in thirty-eight cases negative to 1 : 100 O.T. initially, two were positive to 1 : 1,000 O.T. in the second week, and the other thirty-six negative to both 1 : 1,000 and 1 : 100 O.T. In twenty-five others, similar tests in the first and third weeks yielded no positive results.

This table shows that the measles eruption can suppress the reaction to 1 : 100 O.T., so that, by using this dilution, the fallacy due to the temporary depression of allergy would not be obviated.

Scarlet Fever

The rash of scarlet fever differs from that of measles in being more diffuse but relatively less intense, not leaving such marked staining. As in measles, it is usually the von Pirquet test which has been studied in regard to the possible effects of the exanthem. Rolly (1910) found that in thirty-two allergic subjects six were positive in the acute stage, while twenty-six more became positive in convalescence, suggesting that most cases lost their reaction during the eruptive period. Moltschanoff (1910) obtained similar results. On the other hand, Lereboullet and Baize (1931) mention that in five cases they observed no effect on the von Pirquet test. Mitchell (1928), using the intradermal method, records thirty-one cases in which four out of seven allergic subjects were negative in the acute phase of scarlet fever. Although there is this evidence of an effect on tuberculin sensitivity, the duration of that effect does not seem to have been defined.

Observations in 322 cases of scarlet fever. A group of 322 cases of scarlet fever has been investigated with the Mantoux test in the age period of ten years and under. The majority of the patients were tested in the eruptive stage and thereafter at weekly intervals, usually until the fourth week at

least. In a certain number, however, only a single test could be done. The results are set out in the following table, according to whether the tests were done in acute period or in convalescence. The first week has been taken as the acute period of the disease.

TABLE X

	Results from tests repeated on same group of cases.		Results from single tests on different groups of cases.		
Period of test.	1st week.	2nd week or later.	1st week	2nd week or later.	Total.
Number tested	185	185	38	99	322
Number positive	7	16	8	10	34
Per cent. positive	4 %	9 %	21 %	10 %	10 %

The table shows that 185 cases of scarlet fever were tested both in the acute stage and in convalescence. Seven gave a positive reaction to the initial test, and sixteen were positive to the subsequent tests, indicating that nine had failed to give a positive response in the acute period. This suggests that in about half the cases ultimately proved tuberculin-sensitive, the reaction to the Mantoux test was suppressed at the outset.

The results from the single tests show a higher incidence of positive reactors in the acute period and would suggest no effect on sensitivity by the acute infection, but the same error in sampling applies to these results as in measles.

The varying periods covered by the repetition of the tests from the first week onwards are indicated in the table below.

TABLE XI

Period between initial and final tuberculin tests.

	1st to 2nd week.	1st to 3rd week.	1st to 4th week.	Total
No. of cases tested	22	41	122	185

It will be seen that twenty-two cases were tested in the first and second weeks; in forty-one others tests were continued into the third week, while in the majority (122) the tests were carried on to the fourth week.

Considering only the nine allergic cases who failed to respond to the initial Mantoux test, the negative results obtained from them are classified below, according to the week of disease.

TABLE XII

Period of disease	1st week.	2nd week.	3rd week.	Total.
Negative results in allergic cases	8	1	0	9

This table shows that the reaction to the Mantoux test was suppressed in eight cases in the first week and in one case in the second. These results suggest that in scarlet fever there is a temporary depression of sensitivity, which is usually confined to the first week but can persist into the second week.

The mechanism of temporary hypo-sensitivity. The results obtained from *all* the tests done on the allergic subjects in the first eleven days of the disease are given below.

TABLE XIII

Day of rash	1	2	3	4	5	6	7	8	9	10	11
Positive reactions	—	7	1	2	2	2	—	1	1	—	—
Negative reactions	—	3	2	2	1	1	—	—	—	1	—

This table shows that negative reactions occurred in all but one case in the first week, the greatest incidence being in the first four days. These results are, therefore, closely similar to those obtained in measles. In one instance a negative result in an allergic subject occurred as late as the tenth day.

It will be seen that no tests were done on the first day of the rash, as cases were usually tested the day after admission. On the second day of the rash ten tuberculin-sensitive subjects were tested and the majority gave a positive result, viz. seven positive against three negative. Combining the results on the third and fourth days, there were three positive to four negative results, i.e. the proportion of negative results is greater. On the fifth and sixth days, again, the proportion of negative results falls, there being two negative results to four positive. Granted this is a small series, but the results are suggestive that the greatest effect does not coincide with the onset of the disease, but follows upon the full development of the rash, the greatest proportion of negative results in the allergic subjects being on the third and fourth days, as in measles.

In scarlet fever, no observations were made on cases whose tuberculin sensitivity was already known prior to the onset of the fever.

In order to determine further the possible effect of the rash, the sixteen allergic cases have been divided into two groups, viz. those with a mild rash and those with a moderate or intense eruption.

TABLE XIV

Reaction during scarlet fever.	Type of rash.	
	Mild.	Moderate or intense.
Positive reactions	4	3
Negative reactions	2	7

This table shows that negative reactions were more frequent when the rash was moderate or intense, and suggests that the depression of sensitivity is directly related to the character of the rash.

The possible influence of the patient's own degree of allergy has to be considered. The same results obtained in the acute period are classified in the following table, according to the patient's degree of sensitivity as assessed by the response to the Mantoux reaction in convalescence.

TABLE XV

Reaction during scarlet fever.	Degree of allergy.	
	+ + or less.	+ + + or more.
Positive reactions	4	3
Negative reactions	7	2

In this table the cases are rather unevenly grouped, but it is apparent that negative reactions were more frequent in the less allergic subject. These results, therefore, are similar to those obtained in the larger series of measles cases.   They suggest that the temporary depression of sensitivity is related to the exanthem.   Negative reactions are more likely with the more intense rash, while opposed to this there is the degree of sensitivity possessed by the patient.   The higher the sensitivity, the less likely is the result to be negative.

Chicken-pox

In chicken-pox the lesions are relatively sparse, and therefore in performing the intradermal test, the tuberculin is injected into parts of the skin unaffected by the rash.   Accordingly no analogy can be drawn from the two exanthemata already discussed.

Schonfield (1924), using the von Pirquet test on eight allergic cases, found that in one instance the tuberculin reaction became negative with the onset of varicella, while in four cases the reaction was weakened.   Cozzolino (1925), with the intradermal test, found that in fourteen cases one lost the reaction even to 1 : 100 dilution of tuberculin ; in three the reaction to 1 : 1,000 dilution was weaker in the week following the eruption.

Observations in 191 cases of chicken-pox.   The Mantoux test was applied to 191 cases of chicken-pox.   The majority were tested on one occasion only, but in 76 patients, tests were done during the eruption and later in convalescence, the first week being taken to cover the eruptive phase.   The results are set out in the following table.

TABLE XVI

Period of test.	Results from tests repeated on same group of cases.		Results from single tests on different groups of cases.		Total.
	1st week.	2nd week or later.	1st week.	2nd week or later.	
Number tested	76	76	56	59	191
Number positive	4	5	15	11	31
Per cent. positive	5%	7%	28%	19%	16%

The first part of the table shows that in the seventy-six patients tested, both in the eruptive period and in convalescence, there were four who gave a positive reaction to the initial test in the eruptive phase, while one more reacted to the tests in convalescence.   This one instance of a negative initial test being followed by a positive response later occurred in a girl of 3 years,

who had a moderate discrete rash without any initial fever or complication. A Mantoux test on the sixth day, when the pocks were drying into crusts, was negative; a second test on the nineteenth day, when the crusts had separated, gave a positive response of + + 15 mm. There was no feature of the exanthem to suggest why the initial test was negative.

The results of the single tests classified according to whether they were done in the first week or later, show a higher incidence of positive reactions in the first week. The series of cases is small, however, and deliberate errors in sampling no doubt account for the higher incidence of positive reactions in the eruptive period. They certainly do not indicate any depression of sensitivity in the early stages of varicella.

Results in cases whose sensitivity was already known. In two cases there was an opportunity of observing the effect of chicken-pox on a tuberculin sensitivity already detected and assessed by the Mantoux test prior to the onset of the exanthem.

(i) Case K. L., aged 4 years.

Mantoux test—7 days prior to onset of varicella—+ 20 mm.
,,   ,, —1st day of varicella   —+ 20 mm.
,,   ,, —3rd ,,   ,,   —+ 20 mm.
,,   ,, —13th ,,   ,,   —+ 20 mm.

In this case the tests made before, during, and after the attack of chicken-pox were all identical. With such a close repetition of tests, an increasing response from the stimulating effect of the tests themselves might be expected. This is certainly not evident, and it may be that the varicella had a depressant action, just sufficient to neutralize the stimulating action of the tuberculin injected.

(ii) Case E. H., aged 5 years.

Mantoux test—17 days prior to onset of varicella—+ + +12 : E 13
,,   ,, —5th day of varicella   —+ + +15 : E 25

In this second case there is no evidence of any depression of sensitivity, the reaction obtained in the presence of the chicken-pox rash being as intense and slightly larger than that obtained before.

Diphtheria

Rolly (1910), using the von Pirquet test in twenty-three cases, found that two negative in the acute stage became positive in convalescence. Moltschanoff (1912) found that of fifteen negative in the acute stage, two became positive during convalescence. Mitchell (1928), in fifty-eight cases, found that eight were positive to the Mantoux test in the febrile period, while four more reacted in convalescence, representing an increase from 13·7 to 25 per cent.

Observations in 233 cases of diphtheria. A group of 233 diphtheria patients of ages ranging up to 7 years have been studied: in most cases tuberculin tests were done in the acute stage and also in convalescence from the fourth week onward. In those cases which gave a strong positive response at the

onset the test was not repeated, as the important point to determine was whether tuberculin-sensitive subjects could be actually negative to the Mantoux test in the acute phase. The results are summarized in the following table. As the acute and toxic phases of diphtheria may on occasion last into the second week, where infection has been extensive, the cases have been divided into two groups, viz. those tested in the first fortnight, and those tested after that period.

TABLE XVII

Period of test.	Results from tests repeated on same group of cases.		Results from single tests on different groups of cases.		
	1st fortnight.	3rd week or later.	1st fortnight.	3rd week or later.	Total.
Number tested	105	105	88	40	233
Number positive	7	8	11	6	25
Per cent. positive	6%	7%	12%	15%	11%

The results of the single tests are not conclusive, the difference between 12 and 15 per cent. being not significant in such a small series of cases. There were, however, 105 cases tested both in the acute period and in convalescence. Seven cases gave a positive reaction to the first test, and one more reacted in convalescence. This one instance of an initial negative result being followed by a positive response occurred in a boy of eight years with a mild attack of faucial diphtheria. His reactions were as follows:

Mantoux test— 6th day of disease—negative.

  ,,   ,, —36th ,,   ,, —'late' positive reaction : a response of +10 appeared after an interval of 11 days.

  ,,   ,, —47th ,,   ,, —positive reaction of + + 17 mm.

This patient had a mild afebrile attack of diphtheria, complicated only by an urticarial serum rash on the eleventh day. There was an initial negative result on the sixth day. The next test was in the sixth week, and gave a 'late' positive response, a straight positive reaction being finally obtained in the seventh week. There was no feature of the diphtheria infection to explain either the initial negative or the subsequent delayed response in the sixth week. It may be that the patient was actually in the process of acquiring allergy or that the first two injections were necessary to stimulate a low sensitivity sufficient to react to the third test.

Results in cases whose tuberculin allergy was already known. A more accurate estimate of any effect on allergy was obtained by observing two cases whose degree of sensitivity was known prior to the onset.

(i) Case 33, C. C.—a girl of 6 years.

Mantoux test—11th day before onset of diphtheria—pos.   + 15 mm.

  ,,   ,, — 4th day after   ,,   ,,   —pos.   + 15 mm.

  ,,   ,, —26th day ,,   ,,   ,,   —pos. + + 13 mm.

This was a severe case of faucial diphtheria, yet a test done on the fourth

day of her attack was identical to one done eleven days prior to the onset. This case, therefore, does not show any appreciable effect on sensitivity, even although the attack was a severe one.

(ii) Case 34, B. B.—a boy of 5 years.

Mantoux test—25th day before onset of diphtheria—pos. + + 18 mm.
,,   ,, — 2nd day after   ,,   ,,   —pos. + + 20 mm.

This case had a mild attack of faucial diphtheria. It will be seen that the reaction on the second day was almost the same as the result obtained three weeks before. There is, therefore, no definite evidence that the diphtheria infection had influenced the patient's sensitivity.

It might be, however, that there was a slight effect in these two cases, in so far as the stimulating effect of the previous tuberculin test is not evident in the reaction obtained during the acute stage.

Whooping Cough

Whooping cough is usually classed with measles as a disease particularly apt to lead to tuberculosis, and for that reason its relation to tuberculin sensitivity has claimed attention. Nobécourt and Forgeron (1932) and Galli (1923) obtained results favouring the view that pertussis does depress tuberculin sensitivity, but one finds that the cases in which this effect was observed were commonly complicated either by a pneumonia or an active tubercle infection. Cozzolino (1913), Schlemmer (1914), Lesné and Coffin (1926), and Dumans (1932), on the other hand, have been unable to demonstrate any definite effect.

Whooping cough is a more protracted illness. Its onset is insidious, and the acute stage is usually afebrile, if uncomplicated. Further, it is difficult to determine when the acute phase merges into convalescence.

In the following observations on 415 cases, tests were repeated at intervals of a fortnight to a month to cover the whole period of illness without too many tests. These have been indicated, not by the day, but by the week in which they were done. The results for the whole series are tabulated below. In the group of cases in which only a single test was done, the results are divided according to whether the test was performed in the first two weeks or later, the first two weeks being taken to cover the initial acute catarrhal period of pertussis. In the group of cases in which tests were repeated, the period in which the tests were done is not indicated in this table. These results are considered in relation to the period of the disease in Table XIX.

TABLE XVIII

	Results from tests repeated on same group of cases.		Results from single tests on different groups of cases.		
	1st test.	Last test in convalescence.	1st fortnight.	3rd week or later.	Total.
Number tested	274	274	59	82	415
Number positive	10	14	10	12	36
Per cent. positive	4%	5%	17%	15%	9%

In the foregoing table the incidence of positive reactors in the small group in which only one test was done was similar in both stages of the disease, and suggests no effect on sensitivity in the earlier stages.   In the 274 cases tested on more than one occasion there is a difference : ten were positive to the initial test and four more reacted to a subsequent test.   It is possible that the failure of those four cases to respond to the initial test was related to their attack of pertussis.

The results in these 274 cases on whom Mantoux tests were repeated have been analysed to show the varying periods of the disease covered by the observations.

Table XIX

Period between initial and final tuberculin tests.

	1st to 6th week.	2nd to 6th week.	3rd to 7th week.	4th or later to 10th week.	Total.
No. of cases tested	90	63	56	65	274

It will be seen that in ninety cases the initial test was done in the first week and the final one in the sixth week : similarly there were sixty-three observed from the second to the sixth weeks, and fifty-six from the third to the seventh weeks.   Finally, there were sixty-five in which the initial test was not done until the fourth week or later, these cases being observed till the tenth week.

In Table XX the results of the *initial* tests on the fourteen cases, who proved to be tuberculin-sensitive, are analysed according to the period of the disease.

Table XX

Week of disease.

	1st.	2nd.	3rd.	4th.	5th.	6th or later.	Total.
Positive reactions	4	4	1	1	—	—	10
Negative reactions	—	2	—	1	1	—	4

This table is of value in showing the distribution of the negative reactions in the four cases subsequently proved tuberculin-sensitive.   It will be seen that no negative reactions occurred in the earliest stage, the first week. There were two cases who failed to react to the initial test in the second week, none in the third week, but one in the fourth and another in the fifth week.

In measles and scarlet fever, the two diseases which have been shown to depress tuberculin sensitivity, the effect was manifest in the early acute stage.   In this series of whooping-cough cases the failure to react to the initial test bore no relation to the period of the disease : the negative results were as common in the later stages as in the earlier more acute period.   By analogy with measles and scarlet fever this would not suggest that the pertussis infection was related to these anomalous results.

Although there may be no apparent relation to the acute period of the disease, a consideration of these four tuberculin-sensitive cases, which failed

to react to the initial test, may show some feature of their attack which could explain the phenomenon.   They are summarized as follows:—

(i) Case R. W.—a boy of 10 years.

Mantoux test—2nd week—negative
,,   ,,   —5th   ,,   — + + 20 mm.

This boy had a moderate attack of whooping cough, afebrile throughout, and without complication.

(ii) Case B. B.—a boy of 5 years.

Mantoux test—2nd week—negative
,,   ,,   —7th   ,,   — + + 12 mm.: E. 18.

This child had a severe attack, and at the time of the first test was febrile and suffering from broncho-pneumonia.

(iii) Case E. B.—a boy of 5 years.

Mantoux test—4th week—negative
,,   ,,   —6th   ,,   — + + + 20 mm.: E. 44.

This child had a moderate attack.   In the fifth week he developed an otitis media.   Otherwise his illness was uncomplicated, and at no time was he febrile.

(iv) Case R. F.—a girl of 4 years.

Mantoux test—5th week—negative
,,   ,,   —7th   ,,   — + + 20 mm.

This girl had a moderately severe attack with an initial bronchitis in the first fortnight.   Thereafter her recovery was uncomplicated.   She was afebrile throughout.

Eleven months afterwards tests were repeated as follows:

Mantoux test (1 : 1,000 human O. T.)—negative
A week later—   ,,   ,,   (1 : 1,000 $\overline{aa}$ human and bovine O. T.)— + 12.

These four cases summarized show no feature common to their pertussis infection to explain the initial negative result.   Only one (B. B.) was a severe case, but in that instance the first test was made while the child was suffering from a broncho-pneumonia; failure to respond to the von Pirquet test has been noted by MacNeil (1909) and Rolly (1926), in cases of lobar and broncho-pneumonia.   It is probable that in this case the failure to respond at the outset to the Mantoux test was due to the complicating broncho-pneumonia.

Case R. F. is of particular interest: the same results were repeated a year after the attack of whooping cough, i.e. an initial negative response was followed by a positive.   The only difference was that the initial test made a year after was with human O. T. only, instead of equal parts of human and bovine tuberculin.   It might be suggested that the failure to react to the initial test on the second occasion was due to the fact that human O. T. only was used, and that the patient was actually sensitive only to bovine O. T.   Recent opinion, however, favours the view that the protein is common to both strains of bacilli, and that tuberculin sensitivity is not specific to the strain of the infecting organism.   Accepting this view, it makes these later

results comparable to those obtained whilst the child had whooping cough, and the repetition of events, viz. an initial negative followed by a positive response to the same dilution, when the child was not suffering from any intercurrent acute infection, would suggest that probably the attack of pertussis had no part in the failure to react on the first occasion.

It rather suggests that allergy can wane below a reaction threshold, say, to 1 : 1,000 O. T. intradermally, and then be stimulated above that level by the minute dose of tuberculin of the test itself, so that a subsequent test with the same dilution will be positive.

The two cases, R. W. and E. B., were uncomplicated and afebrile, and there was no feature of the attack to explain the initial negative result. These two cases may have been instances of the phenomenon just described.

The initial negative results were controlled by the fact that typical positive reactions were being obtained in other patients from the same batches of diluted tuberculin.

General Conclusions

The two common exanthemata—measles and scarlet fever—do appear to cause a temporary depression of tuberculin sensitivity as determined by the intracutaneous tuberculin test.   In about half the cases the response to the Mantoux test in 1 : 1,000 dilution was completely suppressed following the onset of the acute infection.   In measles the use of the stronger 1 : 100 dilution for the test was not sufficient to counteract the effect of the exanthem.

This period of depressed allergy or ' hypo-sensitivity ' usually lasts for a week from the appearance of the rash, but in exceptional cases may persist into the second week.   Accordingly, to avoid the possibility of a fallacious negative result in the clinical use of the Mantoux test, at least a fortnight should elapse from the onset of such infections as measles and scarlet fever before a test is done.

The acute infections, chicken-pox, diphtheria and whooping cough could not be shown to have any appreciable effect on tuberculin sensitivity.   On occasion, however, it was found that allergic subjects failed to respond to their initial intracutaneous test.   In one instance, a complicating bronchopneumonia afforded a possible explanation.   In the others, a careful review of the individual cases did not reveal any feature of the acute infection itself likely to explain the anomaly.   This leads one to postulate that in these instances the initial negative response was possibly due to the individual's sensitivity having fallen below the ' reaction threshold ' of the particular dilution of tuberculin used.

It is recognized that the small amount of tuberculin introduced by an intradermal test can stimulate allergy as shown by an increased response to a subsequent test (Debré (1927), Hart (1932)).   Probably the same pheno-

menon occurs in those cases in which an initial test, although negative, is followed by a positive response to the same dilution of tuberculin when the test is repeated a week or two later. Apparently the individual's sensitivity has required the stimulation of a minute dose of tuberculin in order to rise above the reaction threshold of that particular dilution. This illustrates the importance of repeated tests before a negative result to a given dilution can be accepted for diagnostic purposes.

In measles and scarlet fever the depression of sensitivity appears to be due to the action of the rash on the skin itself. For example, in measles the reaction is not lost until the rash is established, even although prodromata have shown systemic infection to be present three or four days previously. Also the maximum effect is found to follow upon the period when the rash is at its height. Further, there is a direct relation between the extent sensitivity is depressed and the intensity of the rash.

Von Pirquet, in his original study of the effect of measles on the scarification test, formed the conclusion that the temporary loss of sensitivity was due, not so much to the influence of the rash on the skin, as to the systemic effect of the measles infection, which either fixed, destroyed, or neutralized the circulating antibodies. He was, of course, at that time assuming that the tuberculin reaction was in some way indicative of resistance to tubercle infection.

Rolly (1910) sponsored the opposite view, that the effect on the tuberculin reaction was due to the action of the rash on the skin. He pointed out that the response to the scarification test could be similarly weakened or even abolished when the skin had previously been irritated with a mustard plaster, tincture of iodine, or cantharides.

The results of this study of the intracutaneous test favour the latter view : namely, that the effect is not a specific one, but is due to local effects of the exanthemata on the skin. It may be said that whichever reaches the skin first—the tuberculin or the measles toxin—will produce its characteristic response.

Once the rash is established the result of a tuberculin test depends on the two opposing factors, the intensity of the rash, and the degree of sensitivity possessed by the subject.

REFERENCES

Cozzolino, O., *Riforma Medica*, Napoli, 1913, xxix. 1203; *La Paediatria*, Napoli, 1925, xxxiii. 561.

Debré, R., and Papp, K., *Compt. rend. soc. de biol.*, Paris, 1926, xcv. 29.

Dickey, L. B., *Amer. Journ. Dis. Child.*, Chicago, 1929, xxxviii. 1155.

Glenny, A. T., Pope, E. C., and Waddington, H., *Journ. Path. and Bact.*, Edinb., 1928, xxxi. 133.

Hart, P. D'A., *Med. Res. Coun. Spec. Rep. Ser.*, No. 164, 1932.

Klein, F., *Beitr. z. Klin. d. Tuberk.*, Berl., 1927, lxvi. 497.

Kollar, I., *Monatschr. f. Kinderh.*, Leipz., 1926, xxxi. 542.

Lereboullet, P., and Baize, P., *Arch. de med. des enf.*, Paris, 1931, xxxiv. 701.

Lesné, and Coffin, *Bull. et mém. Soc. méd. hôp. de Paris*, 1926, l. 787.

Mantoux, C., *Presse méd.*, Paris, 1910, xviii. 10.

McNeil, C., *Brit. Med. Journ.*, Lond., 1909, ii. 1335.

Mitchell, A. G., Wherry, W. B., Eddy, B., and Stevenson, F. E., *Amer. Journ. Dis. Child.*, Chicago, 1928, xxxvi. 720.

Moltschanoff, W. J., *Jahrb. f. Kinderh.*, Berl., 1912, lxxv. 435.

Nobécourt, P., Liège, R., and Herr, A., *Arch. de méd. d. enf.*, Paris, 1930, xxxiii. 65.

Nobécourt, P., and Forgeron, H., *ibid.*, 1922, xxv. 394.

Von Pirquet, C. E., *Berl. klin. Wchnschr.*, 1907, xliv. 1699.

Von Pirquet, C. E., *Münch. med. Wchnschr.*, 1908, xxxiv. 1297.

Rolly, F., *ibid.*, 1910, lvii. 2275.

Schlemmer, A., *Thése de Paris*, 1914.

Schonfield, H., *Monatschr. f. Kinderh.*, Leipz., 1924, xxvii. 602.

Teissier, P., and Léon-Kindberg, M. C. R., *Soc. de Biol.*, Paris, 1911, lxx. 853.

FIG. 1. Case 19. Photograph of forearms on the first day of measles rash. Right arm shows localisation of measles rash at the site of Mantoux test performed twelve days previously. Left arm shows stain of Mantoux reaction from a test done five days before, surrounded by a halo of faint, small, morbilliform macules, and beyond that a localisation of bright maculo-papules.

Mantoux reaction
(24 hrs.)

FIG. 2. Case 19. Photograph of abdomen on the first day of measles rash. Positive Mantoux reaction visible to the right and below the umbilicus, from test done 24 hours previously.
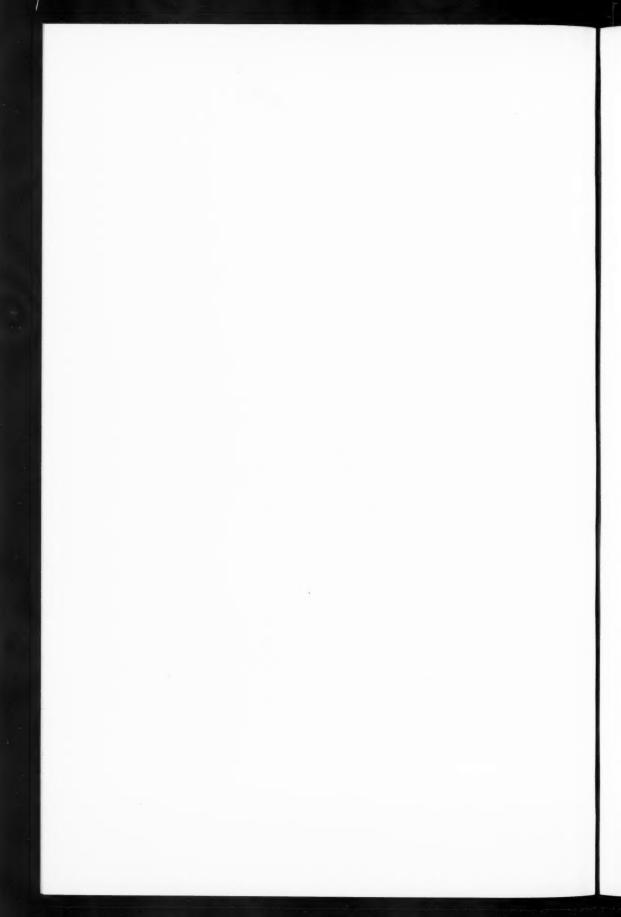
Mantoux test
(4th day)

Mantoux test
(2nd day)

Mantoux reaction
(48 hrs.)

Mantoux reaction
(10th day)

FIG. 3. Case 19. Photograph of abdomen on the ninth day of measles rash. Positive Mantoux reaction (48 hours) visible to the right and above the umbilicus. Stain of positive reaction (tenth day) visible below umbilicus on right side. No evidence of reaction from two tests done to the left of the umbilicus—one on the second and one on the fourth day of the rash.

616.72–002.77

A DIETETIC STUDY OF CASES OF JUVENILE RHEU-
MATIC DISEASE [1]

BY EDWIN C. WARNER AND FRANK G. WINTERTON,
with the help of M. L. CLARK

(From Guy's and the Miller General Hospitals)

Introduction

THE importance of investigating every factor which may contribute to the incidence of juvenile rheumatic disease is warranted by the extent of this condition. In the Ministry of Health *Report* (1927) it was estimated that 0·7 per cent. of the elementary school children in England and Wales, in actual attendance and examined at routine examinations, presented signs of organic heart disease: the condition in probably at least 85 per cent. of these was of rheumatic origin. This compares with the estimate of 1·0 per cent. in New York and 0·52 per cent. in Scotland. With an elementary school population of about 5,000,000, this means that 35,000 children are involved in England and Wales. The Ministry's Report already referred to suggests that some 40 per cent. of the deaths annually ascribed to the various forms of heart disease may be regarded as ultimately traceable to rheumatic infection, so we may estimate that about 25,000 persons die annually in England and Wales from heart disease of rheumatic origin.

All observers of juvenile rheumatism have noticed the tendency of the disease to affect the poorer classes of the population, and many believe that it is the children of the artisan class which are the most affected. Certainly the condition is rare among the more carefully nurtured children of the upper classes. The familial tendency of the disease may be explained on the basis of a hereditary tendency, infection, or a familial dietetic deficiency. Another striking feature is the tendency for the disease to occur in temperate climates, so that it is rare in the tropics and in the arctic regions. But locality alone is not the only important factor: it has been shown at Eton College by Dr. Attlee and at Beaumont College by Dr. O'Ferrall that the incidence is extremely low, while in the elementary school children of Eton and Windsor it is as prevalent as elsewhere. The strikingly low incidence among the English troops in Flanders in the Great War is important as indicating that damp cannot be of major importance. It is invariably

[1] Received February 11, 1935.

accepted that juvenile rheumatism is due to an infection, but the impor-
tance of the individual resistance of the children should not be overlooked,
and it is noticeable throughout how the better-fed children and adults
appear to escape.

The nutritional aspect of resistance to disease has received an impetus in
recent years, particularly as a result of the work of E. Mellanby. In
juvenile rheumatic disease many have suggested that there is a nutritional
factor at work.

The present research was commenced (under the aegis of the Nutrition
Committee of the Medical Research Council) to investigate whether there
is a dietetic deficiency or other factor which may lower the general resis-
tance of children to juvenile rheumatic disease.

The food consumption of rheumatic children has been investigated from
two entirely different points of view. Part I of the present study contains
a record of the food consumed by rheumatic *families* as a whole, and this
has been compared with the food consumed by control families of the same
social stratum. At the same time the individual likes and dislikes of the
children are presented, so that an estimate of the food likely to be consumed
by them is possible. In Part II a detailed record over a period of two days
of the actual food consumed by a small number of the rheumatic *children*
and of suitable control children has been studied. In Part III these results
have been compared with the diets of children in Poor-Law institutions and
of boys at Christ's Hospital, where the rheumatic incidence is low. In
Part IV the expenditure on food and rent is discussed, together with certain
phenomena exhibited by the rheumatic children.

I. *Diets of Rheumatic Families*

By a rheumatic family is meant a family in which at least one child is
suffering from acute rheumatism, chorea, or active carditis; and by a
control family is meant a family in which there has been no history of
juvenile rheumatism in the parents, and no history or evidence on examina-
tion of the disease in any of the children. Suitable families were referred
to one of us (E.C.W.), who made a rigid selection to ensure that these
criteria were fulfilled: some 250 families were inspected in the first
instance to obtain the sixty families finally selected. Children with long-
standing heart disease were excluded, as it was felt that the stunted
growth which so often results might change their food requirements. To
get as accurate data as possible on the likes and dislikes of the children,
families were chosen in which the number of children was not less than two
and not more than four. If there were more than four children the
mother would have very little idea of the individual dietetic peculiarities
of the children: and solitary children are well known to have individual
fancies with regard to food which would be intolerable in larger families.

The members of the group comprising the rheumatic families were poor patients attending the out-patient departments of Guy's Hospital or the Miller General Hospital in South-East London.   A certain number of the children were subsequently admitted to hospital or sent to special institutions for treatment, but prior to this the necessary data were obtained. The control families were of the same social class, drawn from the out-patient departments of the same hospitals; the original disease for which they attended was not of material significance.   In fourteen cases the mothers were in attendance at the ante-natal centre, and brought their children for examination: other children were attending for treatment of fractures, for operations for hernia or circumcision: and five others for straightening irregular teeth or for extraction of a single carious tooth.

The mothers and the children attended the out-patient department of Guy's Hospital and were interrogated and examined by one of us (F.G.W.). Subsequently their homes were visited by the social workers, when any doubtful points were re-investigated, and a note was made of the home conditions and the clothing of the children.

The collection, checking, and analysis of data.   During the two months from mid-January to mid-March, 1931, a record was made of the amount of food consumed by thirty-three rheumatic and twenty-seven control families.   Those months were chosen as they are in the middle of the period when juvenile rheumatic disease is most commonly met.   To obtain the data the parents were given a sheet of paper and asked to set out the quantity and the price of food bought each day.   The diets of two consecutive weeks were thus obtained; as the quantities of food bought were so small, very little food would be left over from one week to the next.   The only exceptions were condiments, pickles, and sauces, but as these have a negligible food value, they will make no material difference.   The mother was visited on an average four times to ensure that the record was accurately kept (and a sum of one shilling was paid for each satisfactory weekly budget).   Where necessary, a record was obtained for a third week.   In only two instances was food home produced (eggs), and this has been included in the weekly budgets; any food such as allowances of milk from charitable sources has also been included.   On the other hand, no allowance has been made for waste, as this is a factor almost impossible to ascertain under the conditions of the present inquiry.

The records were checked in two ways.   First, it was known what types of food were consumed when the mothers were originally interviewed by one of us (F.G.W.); if they did not figure in the weekly budget a special inquiry was made.   Secondly, as the amount of money available for food was known, the amount likely to be spent on food had to compare approximately with the amount actually spent.

In most cases exact quantities were given, but some foodstuffs (oranges, bananas, cabbages, beetroot) were stated in numbers; condensed milk was given in tins; very occasionally the price instead of the weight of a joint

of meat was stated. In all such cases prices and weights were obtained from shops in similar districts and these compared with prices and weights ruling in the households where both were given, and from this double information an estimation was made of weight in the dietaries where this was not known. The same procedure was applied to both rheumatic and control groups, so that the two groups are reasonably comparable. All doubtful points were estimated at the same time and by the same method.

The analytical tables used were those of Plimmer, with some special analyses from other sources.

The number, sex, and age of persons in each household were known. Any meal eaten away from home, or any extra persons present at any meal were noted, and the necessary deduction or addition made to each week's man-value.

It was assumed from previous investigations that the food was about equally distributed between breakfast, dinner, and tea-supper, and accordingly one-third of the man-value for a day has been added or deducted for any meal thus assessed. In comparatively few cases were allowances of this sort necessary, as meals eaten away from home were often from the family larders. In reckoning man-values the Cathcart scale was used:

Man	1·00	Child 8–10	0·70
Woman	0·83	„ 6–8	0·60
Boy 14	1·00	„ 3–6	0·50
Girl 14	0·83	„ 2–3	0·40
Child 12–14	0·90	„ 1–2	0·30
„ 10–12	0·80	„ 0–1	0·20

The rheumatic group contained 92 children (average age 7 9/12th years); the control group 81 (average age 6 11/12th years). The average diet man-value (the only one computed) was 3·56 for the rheumatic and 3·65 for the control group.

Results

(a) *Consumption of protein, fat, carbohydrate, and total calorie consumption.* The results of this study are set out in Table I in terms of man-value per day:

TABLE I

Families.	No. of families.	Protein.	% total calories.	Fat.	% total calories.	Carbo-hydrate.	% total calories.	Total calories.
		grm.		grm.		grm.		
Rheumatic	33	96·5	12·1	109·9	31·4	449·6	56·6	3,261
Control	27	89·8	11·7	108·7	32·0	435·3	56·4	3,164

It will be seen that throughout the rheumatic families consumed more food than the controls. They consumed nearly 100 calories a day more, with an increase in all three classes of foodstuffs.

As it has been repeatedly emphasized that rheumatic disease in children

is essentially a disease of the poorer classes, the present diets have been compared with those in other studies, and in particular with those of different classes of the population (1), (2).

<div align="center">TABLE II</div>

Family income.		Protein.	% total calories.	Fat.	% total calories.	Carbo-hydrate.	% total calories.	Calories.
St. Andrews		grm.		grm.		grm.		
All classes of population	Under £2 10s.	74·9	11·0	93·5	31·3	393·2	57·7	2,779
	£2 11s.–£3 10s.	85·5	11·1	115·9	34·1	424·4	54·8	3,157
	£3 11s.–£5	85·0	10·8	127·6	36·9	412·4	52·3	3,216
	£5–£10	84·4	11·0	125·2	37·1	400·0	51·9	3,136
	£10 and over	99·6	11·4	156·8	40·8	418·6	47·8	3,573
Reading								
Industrial workers	£1–£2	70·9	11·0	91·3	32·0	368·6	57·0	2,640
	£2–£3	74·9	10·5	97·5	31·0	417·3	58·5	2,912
	£3–£4	78·9	10·6	110·1	33·4	418·8	56·0	3,051
	£4 and over	75·9	9·9	120·8	35·7	417·2	54·4	3,132
Cardiff								
Industrial workers	£1–£2	73·7	9·7	101·4	30·4	453·9	59·9	3,091
	£2–£3	78·7	10·3	105·7	31·3	447·7	58·4	3,128
	£3–£4	77·6	10·2	114·4	34·0	425·4	55·8	3,113
	£4 and over	86·2	10·1	140·2	37·2	450·7	52·7	3,494

Family income.	No. of families.	Protein.	% total calories.	Fat.	% total calories.	Carbo-hydrate.	% total calories.	Calories.
Present study								
Rheumatic families	£1–£2	5	89·8	11·8	99·3	29·7	449·5	59·1	3,135
	£2–£3	8	94·1	12·4	104·8	30·8	442·0	57·0	3,173
	£3–£4	16	97·8	12·1	112·7	31·8	448·1	56·2	3,286
	£4 and over	4	104·1	12·1	122·2	33·0	471·6	54·9	3,497
Control families	£1–£2	2	79·1	10·9	84·7	25·8	462·9	63·4	3,011
	£2–£3	15	86·0	11·6	104·5	32·0	418·3	56·4	3,040
	£3–£4	9	95·3	11·8	118·0	33·2	447·9	55·0	3,325
	£4 and over	1	117·3	12·4	136·0	32·6	521·7	55·0	3,885

The amounts of protein, fat, and carbohydrate and the total calories are given separately (Table I). The *total protein intake* of the rheumatic families is higher than in the control group, and the average intake of 96·5 grm. per man is higher than in any other recorded diets, with the exception of the St. Andrews families with an income of over £10 a week, and here it only falls short by 3·1 grm. per man-value.

The *fat consumption* of the rheumatic group is very slightly higher than that of the control group. The amount consumed is 109·9 grm. per day. It has already been shown how a greater total and percentage amount of fat is consumed with a rising income: this is confirmed in the present study and is illustrated in the figures set out in Table II. In the St. Andrews, Reading, and Cardiff studies the amount consumed rises appreciably from 91·3–101·4 to 156·8 grm. when the income is over £10 weekly.

Compared with these figures, the rheumatic and control families studied in this inquiry compare with the poorer families at St. Andrews, Reading,

and Cardiff, and from the point of view of *percentage* of the calories supplied by fat, with the *poorest* families.

The *carbohydrate* intake in the rheumatic families is slightly higher than in the control families, and at 449·6 grm. is almost the highest value recorded. It is very much higher than that of the families at St. Andrews with an income of £10 a week and over, where the carbohydrate consumption was 418·6 grm. per day.

The *total calorie* value of the rheumatic diet is, on an average, nearly 100 calories higher than in the control families. Although it is well below the calorie value of the diet of the better-class families at St. Andrews and Cardiff, it compares favourably with most of the other diets.

TABLE III

Table Showing Distribution of Animal and Milk Proteins and Fats in the Diets: all in Terms of Man-value per day

	Average of 33 rheumatic families.	Average of 27 control families.
Total calories	3,261	3,164
Total protein	96·5 grm.	89·8 grm.
Animal protein	47·0 grm.	43·4 grm.
A.P. as % of total protein	48·0 %	48·2 %
Milk protein	7·8 grm.	7·1 grm.
M.P. as % of total protein	8·2 %	7·7 %
Total fat	109·9 grm.	108·7 grm.
Animal fat	88·8 grm.	81·6 grm.
A.F. as % of total fat	79·7 %	74·4 %
Milk fat	8·5 grm.	7·7 grm.
M.F. as % of total fat	8·0 %	6·8 %
M.F. as % of animal fat	10·2 %	9·0 %

(b) *The distribution of animal foods in the diets.* In any dietetic study the proteins and fats should be examined in greater detail, particularly with reference to the sources of these constituents. Vegetable proteins and fats may form a considerable proportion of the total in some diets because they are so much cheaper. In poorer diets, for example, margarine consisting of vegetable oils may form a large amount of the fat consumed, and yet from a dietetic point of view it is a poor substitute for animal fats, which are more readily absorbed and assimilated, and have a valuable vitamin content. Then again, with reference to proteins, animal proteins are a much more valuable form of food than those of vegetable origin, as they contain all the essential amino-acids in a proportion to one another which is usually close to the proportions needed for growing children.

The only previous reference to this aspect is that of Banning (3), in Holland, who showed that with rising income the amount of animal protein rose from 44 to 55 grm., that is, from 48 to 57 per cent. of the total protein. The results in the present inquiry have been set out in Table III.

The animal protein consumed by the rheumatic families (47·0 grm.) was

higher than that in the control families (43·4 grm.) but as the total protein intake is higher in the former group, the percentages of animal protein to total protein are almost identical.

The amount of milk protein in the rheumatic families (7·8 grm.) is slightly higher than in the control families (7·1 grm.), and correspondingly the proportion of milk protein to total protein is slightly higher in the former.

It should be noted that in both groups of families a considerable amount of the milk protein was in the form of special preparations such as condensed and dried milks.

The amount of animal fat consumed by the rheumatic families was 88·8 grm. as compared with 81·6 grm. consumed by the control families. The percentage of animal fat to total fat was surprisingly high (79·7 and 74·4 per cent. respectively) due probably to the fact that butter has become so much cheaper in the last few years owing to large imports, particularly from Australasia.

The milk fat consumption of the rheumatic families was 8·5 grm., and of the control families 7·7 grm. Here, again, some of the milk fat of the rheumatic and control families was condensed or prepared milk. The main deductions that may be made from this study of animal fat consumption are (1) that the rheumatic and control families consume a good proportion of their fats in the form of animal fats; and (2) the consumption of animal fat and of milk fat by the rheumatic families is rather better than in the control families.

(c) *Analysis of diets with special reference to individual articles of diet.* It has also been possible to analyse the diets further in terms of the individual amounts of milk, potatoes, &c. The records are probably reliable, except in the case of fresh fruit. The amounts stated here are probably minimal, as we know that at times a father would get some fruit out of his own savings which would not appear in the housekeeping records: and again a child may spend an odd penny on fruit bought direct from a shop. The amounts available for the rheumatic and control families are set out in Table IV.

TABLE IV

Table Showing Actual Amounts of Certain Articles of Food in Terms of Man-value per day

	Average of 33 rheumatic families.	Average of 27 control families.
Total calories	3,261	3,164
Fresh milk	0·414 pint	0·379 pint
Condensed milk	0·049 lb.	0·074 lb.
Butter	0·029 lb.	0·022 lb.
Eggs, meat and fish	0·452 lb.	0·430 lb.
Bread	0·709 lb.	0·691 lb.
Sugar	0·168 lb.	0·180 lb.
Potatoes	0·806 lb.	0·714 lb.
Bread, sugar, and potatoes	1·683 lb.	1·585 lb.
Fresh fruit and vegetables	0·552 lb.	0·451 lb.

There is very little difference between the results obtained in the rheumatic and the control families. The rheumatic families consumed rather more fresh milk, butter, eggs, meat and fish, potatoes, bread, and fresh fruit and vegetables: but they consumed less condensed milk and sugar. These results correspond with the generally more liberal diet of the rheumatic families recorded in Section 1 *a*. The only difference which may be of significance is the higher amount of potatoes consumed by the rheumatic families, as this is 12·9 per cent. higher than in the control families.

(*d*) *The individual likes and dislikes of the children for various foods.* The mothers were asked whether the children liked each article of food more than the average (+ +), to an average extent (+), or disliked or refused it (−). The results are set out in the following table (Table V). Only the children of rheumatic age were studied, and although the results were worked out in full, for brevity, the results presented are the only ones likely to be of significance.

The appetite of the rheumatic children appears to be rather below that of the non-rheumatic and control children, as 22 per cent. disliked or refused food as compared with only 7 to 9 per cent.

Milk was available as fresh or heated cow's milk for practically all the children of the rheumatic families, but for only 72 per cent. of the controls. On the other hand, 11 out of the 35 (31 per cent.) rheumatic children disliked or refused it, compared with 4 of the 26 (15 per cent.) non-rheumatic children, and 5 of the 33 (15 per cent.) controls. Milk at school was drunk by 50–52 per cent. of the rheumatic and non-rheumatic children as compared with 33 per cent. of the control children. *Butter* was eaten less readily by the rheumatic children, and *cheese and bacon* less readily by the rheumatic and non-rheumatic children as compared with the controls. *Cream* appears to have been less often available for the rheumatic families. *Condensed milk, margarine, dripping, eggs, and cod-liver oil* showed no material difference between the three groups.

Meat was eaten readily by about a quarter of the rheumatic children and disliked or refused by a half: compared with the other groups the rheumatic children were rather less fond of meat. *Fresh fish* was more commonly disliked or refused by the children of the rheumatic families; and *tinned fish*, although available for between a half and a third of the children, was less readily taken by the rheumatic children. *Liver, sausages, and meat pies* showed no differences in the groups.

Porridge and jam were less in demand among the rheumatic children as compared with the others; and *prepared cereals, milk-puddings, and onions* were less readily taken by the rheumatic and non-rheumatic children as compared with the controls. On the other hand, *potatoes* were more readily consumed by the rheumatic children, and *sugar* more readily by the rheumatic and non-rheumatic children.

TABLE V

Likes and Dislikes for Various Articles of Food.   Boys aged 7–11 and Girls aged 7–12

	Rheumatic children.				Non-rheumatic children of rheumatic families.				Children of control families.			
No. of children	36				27				46			
	No. partaking of food.	Appetite.			No. partaking of food.	Appetite.			No. partaking of food.	Appetite.		
		++ 28%	+ 50%	− 22%		++ 19%	+ 74%	− 7%		++ 24%	+ 67%	− 9%

Dairy products and foods consisting mainly of fats.

		%	%	%		%	%	%		%	%	%
Milk—												
Fresh	17	18	41	41	17	12	64	24	23	26	52	22
Boiled or scalded	18	11	67	23	9	0	100	0	10	20	80	0
Condensed	20	5	95	0	17	6	94	0	26	0	85	15
At school	18				14				15			
Butter	24	17	83	0	16	31	69	0	23	39	52	9
Cheese	32	3	81	16	23	4	83	13	36	36	61	3
Bacon	34	0	65	35	24	0	79	21	42	19	69	12
Cream	8				6				18			

Margarine, dripping, eggs, and cod-liver oil showed no significant difference.

Foods mainly consisting of protein.

Meat	36	22	25	53	27	15	44	41	46	7	63	30
Fish—												
Fresh	32	12	44	44	24	12	47	41	40	30	48	22
Tinned	15	7	40	53	9	22	45	33	20	50	40	10

Liver, sausages, and meat pies showed no significant difference.

Foods mainly consisting of carbohydrates.

Porridge	31	6	46	48	24	17	46	37	39	13	64	23
Jam	36	6	61	33	26	8	80	12	45	4	82	14
Prepared cereals	12	25	25	50	8	37	0	63	12	59	33	8
Onions	34	12	53	35	27	11	48	41	46	20	65	15
Milk puddings	35	23	51	26	25	28	44	28	42	45	46	9
Potatoes	36	22	66	12	27	15	56	29	46	22	52	26
Sugar	36	44	48	8	27	44	41	15	46	22	63	15

Bread, toast, biscuits, boiled sweets, marmalade, treacle and honey, beetroot, parsnips, carrots, turnips, fresh vegetables, cooked vegetables (as peas, beans, marrow, greens) fresh and stewed fruits, were all taken as readily by the three groups of children.

Condiments.

Vinegar	31	26	48	26	25	16	60	24	39	26	43	31
Mustard	26	0	19	81	19	5	16	79	35	9	51	40

Pickles and sauces were equally well taken by the three groups of children.

+ + represents a liking for the food above the average.
 + represents an average liking for the food.
 − represents a dislike or refusal of the food.

II. *The Actual Consumption of Food by Rheumatic Children compared with that of Non-rheumatic and Control Children : and also compared with that of the Rheumatic and Control Families.*

Part II records the actual daily consumption of a small number of the children studied in Part I. The term 'rheumatic child' has the same meaning as in Part I : a 'non-rheumatic child' is a non-rheumatic member of the rheumatic families : and a 'control child' is a child of the control families.

Following the 1931 inquiry detailed in Part I, Miss Clark visited the homes of nine of the original rheumatic and eight of the control families, choosing those where the co-operation of the parents was certain. The results have been published separately (4). She has kindly allowed the use of these data, for the collection of which she was responsible. For each of two days a detailed record was kept of the actual food intake of each member of the family. This inquiry was undertaken in the Winter 1932–3, at a time when many of the rheumatic children had recovered from their attacks. This new series of data represents the consumption of food by *rheumatic children* who were in many cases in comparatively good health, and thus differs from the data so far discussed, which represent the food consumption of *rheumatic families* of which some of the children were in an early stage of rheumatic disease. As a whole there is a very close correspondence between the diets of the families in the 1931 study and the 1932–3 study.

The present records represent the actual consumption of food by the children. To make the comparison as close as possible, all the children are between the ages of five and fifteen years.

The numbers involved are averages of a much smaller series of figures than were used for the family diets considered above, which were constructed from *weekly* records, and on the whole the families represented the better classes of the 'rheumatic' and 'control' families, as they co-operated more readily, and their data were more reliable.

The rheumatic children consume 3,205 calories a day, which is slightly higher than in the case of the non-rheumatic and control children (3,160 calories). They appear also to get a good proportion of the food available in the rheumatic families.

The total and the animal proteins consumed show little difference between the two groups of children, but the total protein intake at 86·2 grm. is over 10 grm. less than that available in the rheumatic families : and in the same way the animal protein intake at 37·4 grm. is nearly 10 grm. less than that in the rheumatic families.

The total and the animal fat consumption is in each case higher in the rheumatic children (120·6 grm. and 100·1 grm.) than in the non-rheumatic and control children (115·0 grm. and 94·3 grm.). Compared with that consumed by the rheumatic families and the control families, it appears as if

the rheumatic children get rather more than their share as they consume between 10 and 11 grm. more than the rheumatic families.

The total carbohydrate intake in the case of the rheumatic children (422·1 grm.) shows little difference from the non-rheumatic and control children (425·1 grm.): although the intake is rather less than the amount allowed by the family averages (449·6 and 435·3 grm.), the difference is probably of little significance.

<div align="center">TABLE VI</div>

Showing the Actual Consumption of Certain Articles of Food by Rheumatic Children (Average 10–10/12th Years—Average Man-value 0·78), and by Non-rheumatic and Control Children (Average Age 9–10/12th Years—Average Man-value 0·74): and a Comparison of these with the Family Food Consumption. All Results Expressed in Terms of Man-value Equivalents per Day

	Average of 9 rheumatic children.	Average of 25 non-rheumatic and control children.	Average of 33 rheumatic families.	Average of 27 control families.
Total calories	3,205	3,160	3,261	3,164
Total protein	86·2 grm.	84·7 grm.	96·5 grm.	89·8 grm.
% of total calories	11·0 %	11·0 %	12·1 %	11·7 %
Fat	120·6 grm.	115·0 grm.	109·9 grm.	108·7 grm.
% of total calories	35·0 %	33·8 %	31·4 %	32·0 %
Carbohydrate	422·1 grm.	425·1 grm.	449·6 grm.	435·3 grm.
% of total calories	54·0 %	55·2 %	56·6 %	56·4 %
Animal protein	37·4 grm.	38·6 grm.	47·0 grm.	43·4 grm.
% animal prot. to total prot.	43·4 %	45·6 %	48·0 %	48·2 %
Animal fat	100·1 grm.	94·3 grm.	88·8 grm.	81·6 grm.
% animal fat to total fat	83·0 %	82·9 %	79·7 %	74·4 %
Fresh milk	0·51 pint	0·49 pint	0·41 pint	0·38 pint
Butter ·	0·048 lb.	0·041 lb.	0·029 lb.	0·022 lb.
Eggs	0·026 lb.	0·027 lb.	—	—
Fresh meat	0·26 lb.	0·23 lb.	—	—
Bread	0·69 lb.	0·73 lb.	0·71 lb.	0·69 lb.
Sugar	0·105 lb.	0·134 lb.	0·17 lb.	0·18 lb.
Potatoes	0·76 lb.	0·58 lb.	0·81 lb.	0·71 lb.
Fresh fruit and vegetables (excluding potatoes and tinned fruit)	0·54 lb.	0·46 lb.	0·55 lb.	0·45 lb.
Raw fruit and raw tomatoes	0·15 lb.	0·105 lb.	—	—
Calories from milk and butter/ calories from bread, sugar, and potatoes	29·9 %	26·7 %	18·7 %	16·6 %

An analysis of the *individual articles of food* shows that the rheumatic children consume more milk (0·51 pint) and more butter (0·048 lb.) than the non-rheumatic and control children (0·49 pint and 0·041 lb.), and also as compared with the family consumptions (0·41 pint and 0·029 lb.). These results are the opposite to what might be expected from the study of the likes and dislikes of the children, where milk and butter were more commonly disliked by the rheumatic children. The bread consumption shows

similar values in all the studies, but the sugar consumption of the rheumatic children (0·105 lb.) is lower than the non-rheumatic and control group (0·134 lb.) and also as compared with the family consumptions (0·17–0·18 lb.). This again is the opposite to the findings from the likes and dislikes of the children. Although the amount of potatoes (0·76 lb.) is not excessive compared with the family consumptions (0·71–0·81 lb.), the rheumatic children consume distinctly more than the non-rheumatic and control children (0·58 lb.) : a finding which agrees with the larger consumption of the rheumatic families, and with the distinct liking shown by the rheumatic children for this class of food.

III. *A Comparison of the Diets of the Rheumatic Families and Rheumatic Children with those of Children in Poor-Law Institutions and at Christ's Hospital.*

For comparison with the preceding results two groups of children have been chosen where rheumatism is of infrequent occurrence. Benjamin showed (5) that in Poor-Law Institutions the incidence of juvenile rheumatism is very low. He found only nineteen cases in a total population of 1,872 (1·0 per cent.), and of these five cases had had rheumatism prior to admission. This contrasts with 3·6 per cent. of children affected in the elementary school population of England and Wales. The children in these institutions were drawn from the same poor class of the population as the children studied in the present report, and these children were in contact with a certain number of children with active rheumatism, yet ' no evidence of infection from one case to another could be found '. With the help of Dr. Thomas and Dr. Wilfred Sheldon the diets of three of the schools previously investigated by Benjamin, were examined. The diets were taken from the issues of the stores departments, for a week in each case, and the months chosen were those of February in 1927 and 1928. (This was during the time these same homes were still under the care of the Boards of Guardians, and about the same time as Benjamin's inquiry.) In any case it was found that there was very little variation from one week to another, particularly when the weeks of corresponding months from one year to another were studied. To facilitate comparison, the average age of the children was known ($9\frac{5}{12}$ years) and the diets converted to man-value equivalents.

At Christ's Hospital there is an average population of 800 boys who enter the school between the ages of nine and twelve and who leave between sixteen and nineteen. Dr. G. E. Friend (6) has kept a careful record of the diet of these boys over a period of twenty years, and a corresponding record of the incidence of juvenile rheumatism. He has very kindly allowed the use of his results in the present study. What makes a study of these particularly valuable is that the food has been varied at the end of the periods 1913–17, 1918–22, 1923–27, and 1928–32, while during each of these five-yearly periods the diet has been fairly constant : also there is a wide

TABLE VII

Showing the Consumption of Food by the Rheumatic Families, by 9 Rheumatic Children (Average Man-value 0·78), by Children in Poor-Law Institutions (Average Age 9–5/12th Years and Average Man-value 0·70), and by Boys at Christ's Hospital in Lent Terms (Average Age 13–11/12th Years and Average Man-Value 0·90). All Results Expressed in terms of Man-value Equivalents.

	Average of 33 rheumatic families.	Average of 9 rheumatic children.	Average of 1,870 children in Poor-Law institutions.	Average of 800 boys at Christ's Hospital—Lent Terms.			
				1913–1917	1918–1922	1923–1927	1928–1932
Total calories	3,261	3,205	3,169	2,843	3,067	3,179	3,448
Total protein	96·5 grm.	86·2 grm.	98·1 grm.	88·8 grm.	97·1 grm.	107·1 grm.	107·3 grm.
% of total calories	12·1 %	11·0 %	12·7 %	12·0 %	13·0 %	13·8 %	12·8 %
Fat	109·9 grm.	120·6 grm.	94·9 grm.	74·5 grm.	81·9 grm.	105·2 grm.	120·4 grm.
% of total calories	31·4 %	35·0 %	27·7 %	24·0 %	24·8 %	30·8 %	32·5 %
Carbohydrate	449·6 grm.	422·1 grm.	459·6 grm.	437·0 grm.	465·0 grm.	430·0 grm.	460·0 grm.
% of total calories	56·6 %	54·0 %	59·6 %	63·0 %	62·2 %	55·4 %	54·7 %
Animal protein	47·0 grm.	37·4 grm.	42·6 grm.	—	39·2 grm.	53·2 grm.	54·1 grm.
% of animal prot. to total prot.	48·0 %	43·4 %	39·9 %	—	40·4 %	49·6 %	50·4 %
Animal fat	88·8 grm.	100·1 grm.	82·2 grm.	—	50·6 grm.	94·6 grm.	103·6 grm.
% of animal fat to total fat	79·7 %	83·0 %	85·2 %	—	61·7 %	90·0 %	86·0 %
Fresh milk	0·41 pint	0·51 pint	1·01 pint	—	0·48 pint	0·73 pint	0·86 pint
Butter	0·029 lb.	0·048 lb.	0·031 lb.	—	0·00 lb.	0·070 lb.	0·098 lb.
Eggs	—	0·026 lb.	—	—	—	—	—
Bread	0·71 lb.	0·69 lb.	0·93 lb.	—	1·05 lb.	0·89 lb.	0·75 lb.
Sugar	0·17 lb.	0·105 lb.	0·108 lb.	—	0·074 lb.	0·087 lb.	0·101 lb.
Potatoes	0·81 lb.	0·76 lb.	0·67 lb.	—	0·61 lb.	0·51 lb.	0·55 lb.
Fresh fruit and vegetables (excluding potatoes and tinned fruit)	0·55 lb.	0·54 lb.	0·39 lb.	—	0·21 lb.	0·29 lb.	0·41 lb.
Cals. from milk and butter/Cals. from bread and sugar and potatoes	18·7 %	29·9 %	34·1 %	—	12·4 %	40·7 %	56·5 %
No. of cases of rheumatism	—	—	19 (1·0 %)	17 (2·1 %)	19 (24 %)	9 (1·1 %)	6 (0·75 %)

variation between the figures in the years of the War and the period immediately following, when food was scarce, as compared with the later periods. There is a tendency for rheumatism to occur in waves every few years, but the choice of five-yearly periods tends to minimize this. Owing to the unsuitability of the climate for cases of rheumatism the parents of any boys showing this tendency at the entrance medical examination have always been advised not to allow their boys to enter: but this applies equally to the four five-yearly periods. The results obtained are recorded in Table VII, and all results are expressed on the man-value basis. (The incidence of rheumatism in the schools has been recorded at the bottom of this table.)

The *calorie* intake of the rheumatic families (3,261) and of the rheumatic children (3,205) is larger than that of the Poor-Law children (3,169) and compares favourably with that of the boys at Christ's Hospital (2,843, 3,067, 3,179, and 3,448). It may fairly be concluded that there is no deficiency in total calorie intake in the rheumatic children—but it should be noticed that the fall in the incidence of rheumatism in the population at Christ's Hospital corresponds in some measure with the rise in total calorie intake.

The *total protein* intake of the rheumatic children (86·2 grm.) is lower than that of the rheumatic families as a whole (96·5 grm.), the Poor-Law children (98·1 grm.), and the four periods at Christ's Hospital (88·8 to 107·3 grm.): also the rise from 88·8 and 97·1 grm. in the first two periods at Christ's Hospital to 107·1 and 107·3 grm. in the third and fourth periods corresponds with the drop in the rheumatic figures. The same applies to the *animal protein* intake, as the lowest values were recorded in the rheumatic children (37·4 grm.) and in the second period at Christ's Hospital (39·2 grm.): whereas in the Poor-Law schools (42·6 grm.) and in the later periods at Christ's Hospital the values were substantially larger (53·2–54·1 grm.). The smaller protein intake in the children with the greatest incidence of rheumatism is due almost entirely to a smaller quantity of animal protein. In passing, it is of interest to note how in all studies of protein intake the calories supplied by protein form about 12 per cent. of the total calorie intake, and this is shown also in Table II. This must be an expression of some basic biological principle.

There appears to be no direct relationship between the *total fat* intake and the incidence of rheumatism. The rheumatic families (109·9 grm.) and the rheumatic children (120·6 grm.) have the highest intake, and considerably more than in the Poor-Law children (94·9 grm.). The values at Christ's Hospital are very low in the first two periods (74·5 and 81·9 grm.) corresponding with the highest period of rheumatism, and rise to 105·2 and 120·4 grm. in the succeeding periods which show a lower rheumatic incidence. The *animal fat* intake is high in the rheumatic children (100·1 grm.) and attains a high value in the rheumatic families (88·8 grm.): whereas in the Poor-Law children the value is only 82·2 grm., but here, again, with the very low intake of animal fat in the earlier period at Christ's Hospital (50·6 grm.) we have the

highest incidence of rheumatism, and when the value is doubled in the third and fourth periods (94·6 and 103·6 grm.) the incidence is materially lessened. Also it may be noted that where the percentage of animal fat to total fat is highest, the rheumatic incidence tends to be lower.

The consumption of certain *individual articles of diet* is also shown. It is a very striking fact that the lowest intake of *fresh cow's milk* corresponds with a high proportion of rheumatism. The rheumatic families (0·41 pint), the rheumatic children (0·51 pint), and the boys in the second period at Christ's Hospital (0·48 pint), consume much less than in the Poor-Law Institutions (1·01 pint) and in the third and fourth periods at Christ's Hospital (0·73 and 0·86 pint). In the case of the rheumatic families and the rheumatic children we must add to this amount of fresh cow's milk, condensed milk, much of which was condensed skim milk. The man-value consumption of this by the rheumatic families was 0·049 lb. per day, but the food value of this kind of milk is not to be compared with that of fresh cow's milk. *Butter* was consumed in quantities of 0·048 lb. by the rheumatic children, which is higher than in the rheumatic families (0·029 lb.) and the children in the Poor-Law Schools (0·031 lb.). On the other hand, the rise in consumption from nil to 0·098 lb. at Christ's Hospital corresponds with the considerable fall in the incidence of rheumatism. The amount of *bread* consumed is much the same in the rheumatic families (0·71 lb.), the rheumatic children (0·69 lb.), and in the fourth period at Christ's Hospital (0·75 lb.): whereas in the Poor-Law Schools (0·93 lb.) and in the periods of higher incidence at Christ's Hospital (1·05 and 0·89 lb.) the amount of bread rose to the highest figures. There seems, therefore, to be no relationship between the bread consumption and the rheumatic incidence. The same applies to the *sugar* consumed, where no relationship between this and the rheumatic incidence can be found. The *potato* ration is highest in the rheumatic families (0·81 lb.) and the rheumatic children (0·76 lb.), which compares with 0·67 lb. for the Poor-Law children. Also at Christ's Hospital the highest incidence of rheumatism in the second period corresponds with an intake of 0·61 lb. which is a higher consumption than in the third and fourth periods (0·51 and 0·55 lb.). The amount of *fresh fruit and vegetables* (excluding potatoes and tinned fruit) shows the highest values in the rheumatic families (0·55 lb.) and the rheumatic children (0·54 lb.)—values which are distinctly higher than in the Poor-Law Schools (0·39 lb.): on the other hand, the diet at Christ's Hospital shows a rising amount from 0·21 lb. to 0·41 lb. from the earlier to the later periods, but even this latter figure is far short of the consumption of the rheumatic families and the rheumatic children. It is of interest to compare the ratio of the calories derived from milk and butter with those from bread, sugar, and potatoes as this gives a rough value of what might be termed a ' rachitic ratio '. The value in the rheumatic children (29·9 per cent.) is rather lower in the Poor-Law children (34·1 per cent.) ; and the striking rise from 12·4 per cent. to 56·5 per cent. at Christ's Hospital again corresponds to the striking fall in rheumatic disease.

IV.   *Other Criteria*

1. Despite the difficulty of discovering accurately the amount of *income* in any given family, an attempt was made to compare the income and mode of expenditure of the rheumatic and control families.   The tables are omitted.   The actual income was very difficult to ascertain, but we were able to obtain figures expressing the amount the mother was given to spend ; this was 52*s*. for the rheumatic families and 50*s*. 10*d*. for the control families, and included the payment for rent and insurance as well as for food and clothing.   Of this, the rheumatic families spent 30*s*. 5*d*. on food (58·5 per cent.) and 10*s*. on rent (19·2 per cent.) and the control families 27*s*. 5*d*. on food (54·0 per cent.) and 12*s*. 7*d*. on rent (24·7 per cent.).   In other words, the rather better feeding already recorded in the rheumatic families is also expressed in a greater percentage expenditure on food.

2. It has been stressed by various observers, particularly by Vining, that rheumatic children exhibit *certain phenomena* such as nervousness, attacks of feverishness, disturbed sleep, for some months before the attack of rheumatism occurs.   As most of the rheumatic cases were early cases, the mothers were questioned with reference to these symptoms in all the children examined.   In both boys and girls, excitability, ' wasting ', sweating, head-aches, and attacks of abdominal pain were much more frequently complained of in the rheumatic children : whereas ' nervousness and listlessness ' were symptoms complained of with particular frequency in the rheumatic girls but not the boys.   Attacks of pallor and enuresis were much more commonly met in the rheumatic families, but about equally in the rheumatic and non-rheumatic members.

3. The mothers were asked the actual hours of *sleep* of the children in their own homes, and also whether the sleep was disturbed or not.   The months in which these data were collected were May to January, so that most data refer to the summer and winter months and none to the spring months of the year.   It is, of course, quite impossible to check the mother's statements in this instance.

From the results of our questionnaire it appears that the hours of sleep in the three groups are all much the same, all the averages lying between 11·0 and 12·0 hours a night.   On the other hand, among the rheumatic girls there is a much greater tendency to lie awake and not be able to get to sleep (30 per cent.), to sleep ' restlessly ' or ' lightly ' (30 per cent.), and to get night terrors (13 per cent.).   The night terrors recorded here referred to any symptoms of this within the preceding three years.

Discussion, Summary, and Conclusions

To-day rheumatic disease is the commonest cause of disability among children.   It is peculiar in its special tendency to affect the poor, and in being familial.   Investigations of the housing and similar conditions have

largely been negative. On the other hand, as H. F. Swift has recently remarked (7), ' loss of weight has been found to be one of the most common precursors of a relapse of rheumatism '—a view with which we heartily concur, and this in itself is suggestive of a failure of nutrition.

The actual income of the families, including payment for rent, insurance, &c., was 52s. for the rheumatic families and 50s. 10d. for the control families. Of this, the rheumatic families spent 30s. 5d. on food, and the control families 27s. 5d. on food. The rheumatic families had 3,261 calories per man per day, and the control families 3,164 calories. These figures compare favourably with the previous dietetic studies at St. Andrews, Reading, and Cardiff, and the caloric value was better than for the families at St. Andrews with incomes between £5 and £10, and at Reading with incomes of over £4. From the point of view of total calories, the mothers spent their money extremely well, and there was no sign of under-nutrition in the rheumatic families as a whole.

When we compare the heights and weights of the rheumatic and control children with one another and with the tables given by Greenwood (8) we find the rheumatic children are up to the normal standard of physical development of English school-children. Although according to the mothers' statements the appetite of the rheumatic children was rather poorer than that of the non-rheumatic and control children, on the man-value basis the calorie consumption of the nine rheumatic children (3,205) is little less than their share as judged by the intake of the families as a whole (3,261) and is in slight excess of that of the twenty-five non-rheumatic and control children (3,160), the Poor-Law children (3,169) and the boys during the first two periods at Christ's Hospital (2,843–3,067). On the other hand, the rise in the calorie consumption in the third and fourth periods in Christ's Hospital to the high figure of 3,448, corresponds to the fall in the incidence of rheumatism. On the whole it appears as if the rheumatic families and rheumatic children have a sufficient calorie intake.

The total protein available for the rheumatic families is higher than in the control families ; the animal protein intake of the rheumatic families is also higher than in the control families. The fact that the rheumatic children consume only 86·2 grm. of total protein and 37·4 grm. of animal protein on the man-value basis shows that neither they nor the control children (84·7 and 38·6 grm.) get their full share in the family diet. The deficiency is entirely in the animal protein which is 5 grm. less than that of the Poor-Law children and 16 grm. less than in the later periods at Christ's Hospital. This corresponds with the mothers' statements that the rheumatic children were less fond of meat and fresh fish. When the animal protein (and therefore the total protein) rises by about 15 grm. at Christ's Hospital from the second to the fourth period, the incidence of rheumatism correspondingly falls. It has always been recognized that children need more than their man-value equivalent of animal protein, and this has been re-emphasized again recently (9), but in practice the father's share is always

above the man-value equivalent.   This bears out Vining's statement that rheumatic children have a dislike for, and probably do not consume sufficient, animal protein : but this applies almost equally to all the children of the families of this social stratum.

The consumption of total fat and of animal fat by the rheumatic families is rather higher than in the control families, and is much the same as in the poorer families at St. Andrews, Reading, and Cardiff, but it is much less than in the better class families at St. Andrews.   Rheumatic children consume rather more of both total fat and animal fat available than the non-rheumatic and control children, and correspond with the amounts for the boys at Christ's Hospital.   So that although the amount of fat consumed is at a fairly high level, it is not so high as in the better class families. The amount of fresh cow's milk consumed is about the same in the rheumatic children and the non-rheumatic and control children, but is strikingly less than in the Poor-Law Schools and the later periods at Christ's Hospital. Whereas 31 per cent. of rheumatic children dislike or refuse this form of milk, only 15 per cent. of the non-rheumatic and control children do so, confirming the findings of Arbour Stephens.   In this connexion, a recent committee of the Ministry of Health (10) has reported that children should have one pint of milk daily per child.   The butter consumption of the rheumatic children is considerably more than the consumption of the non-rheumatic families, and is more than that of the Poor-Law children, but is much less than in the later periods at Christ's Hospital.   Therefore although the rheumatic children consume a moderate amount of fat, the amount of fresh dairy products (and especially milk) is at a much lower level than in the other classes of children, and they also tend to dislike fresh milk and butter.   Of the fresh milk given half the rheumatic families took it after scalding or boiling.   But perhaps the most striking fact suggesting that an increase in the animal fat in the form of fresh milk and butter may be of prophylactic value, is furnished by the figures from Christ's Hospital where the incidence of rheumatism was reduced to less than a third, corresponding to a rise in the animal fat consumption from 50·6 to 103·6 grm.—due largely to an increase in the rations of milk and butter.

The consumption of carbohydrates is slightly higher in the rheumatic families than in the control families and is nearly the highest recorded when compared with the families at St. Andrews, Reading, and Cardiff. Neither the rheumatic nor the non-rheumatic and control children consume their man-value equivalents.   This is much less than the children in the Poor-Law Schools, and as compared with the better periods at Christ's Hospital.   The high value in the Poor-Law Schools was mainly due to a large consumption of bread, but no direct relationship between this and the incidence of rheumatism could be traced.

On the other hand, more potatoes were consumed by the rheumatic families and the rheumatic children than the control families, the control children, the children in the Poor-Law Schools, and at Christ's Hospital—

this being due in part to a craving for potatoes on the part of the rheumatic children. The ratio of calories from fresh milk and butter to calories from bread, sugar, and potatoes gave a value of 29·9 per cent. for the rheumatic children, and 26·7 per cent. for the non-rheumatic and control children. This ratio rose from 12·4 per cent. in the rheumatic to 56·5 per cent. in the non-rheumatic period at Christ's Hospital.

In view of the recent work of Rinehart (10) suggesting that a deficiency of vitamin C is responsible for the rheumatic diathesis, it is of interest to note that the consumption of fresh fruit and vegetables by the rheumatic children and the rheumatic families is much higher than in the Poor-Law Schools and at Christ's Hospital even in the period with the lowest rheumatic incidence.

From the above study it cannot be claimed that any one factor can be incriminated as a contributory cause for rheumatism occurring in certain families and certain children. It does appear, however, that the consumption of animal protein and of dairy products by the rheumatic children and by the control children of this social status is low, and the intake of carbohydrate, particularly in the form of potatoes, is high. We have tried the effect of adding extra vitamin A and vitamin D in the form of Radiostoleum as a prophylactic agent; as this was of little value, it does not appear that the imbalance of fats and carbohydrates was working through these agents.

REFERENCES

1. *Med. Res. Coun. Spec. Rep. Ser.*, Lond., 1931, No. 151.
2. *Ibid.*, No. 165.
3. Banning, C., *Act. Brevia Neerland.*, Amsterdam, 1931, i. 29.
4. Clark, M. L., *Brit. Med. Journ.*, Lond., 1933, ii. 977.
5. *Med. Res. Coun. Spec. Rep. Ser.*, Lond., 1927, No. 114, 80.
6. Friend, G. E., *The Schoolboy: a Study of his Nutrition, Physical Development and Health*, Cambridge, 1935.
7. Swift, H. F., *Amer. Heart Journ.*, St. Louis, 1930–31, vi. 625.
8. Greenwood, A., *The Health and Physique of School Children*, Lond., 1913.
9. *Lancet*, Lond., 1934, i. 1099.
10. *Ministry of Health Report*, ' The Criticism and Improvement of Diets ', 1931.
11. Rinehart, J. F., Connor, C. L., and Mettier, S. R., *Journ. Exper. Med.*, N. York, 1934, lix. 97.
12. Warner, E. C., *Arch. Dis. Child.*, Lond., 1932, vii. 273.

OBSERVATIONS ON THE THERAPEUTIC USE OF IODIDES [1]

By W. R. SNODGRASS

(From the Western Infirmary, Glasgow)

I. *Historical and Introductory*

(a) *The employment of iodides in the treatment of syphilis.* This work was undertaken because, on reviewing the literature, it was found that very few clinical studies of recent date had been published. The text-books of 1923 exhibited a remarkable unanimity in their advice. Thus Harrison, Hazen, Clarkson, White, Jeanselme, Rolleston, Browning and McKenzie, Browning and Watson, Osler and McRae suggest that the potassium salt be given orally in doses of 10 to 15 grains thrice daily over short periods of time, and indicate that the special value of the drug is to be found at the outset of the treatment of tertiary cutaneous lesions, and during the intervals between courses of treatment by the arsenical substitutes and the heavy metals. In the pharmacological and therapeutic text-books, such as those of Poullson, Cushny, Hale, White, and Bruce and Dilling, similar advice is offered.

A search was therefore made of the earlier literature in order to determine the clinical foundations upon which such views were founded. The earliest reference which has so far been traced, is that found in an article by Jacques Coster (1) in 1823, where the following paragraph occurs :

' M. Biett, profiting by the opinion expressed by M. Coindet of Geneva on the supposed value of potassium iodide against inflammatory lesions of a syphilitic nature, made a great many observations in the Hospital Saint-Louis in cases of venereal ulcer. He is the first, I believe, who has combined iodine with mercury in this sort of affection. Brera (2), a celebrated professor of Padua, published a book containing the results of investigations made by him in a hospital in that city, over a period of two years.'

Many early references are to be found in the volume *Iodotherapie*, written by A. A. Boinet and published in 1855 (3). There (p. 5) he definitely states that M. Coindet of Geneva delivered the first paper on July 25, 1820, on the use of iodine in goitrous cases. This followed upon the demonstration of iodine in sea-water, in burnt sponges, and in burnt seaweed. Buisson (4), in 1825, wrote a thesis on the use of iodine in syphilis.

Numerous papers in all countries rapidly followed upon these discoveries,

[1] Received February 20, 1935.

but the first man to establish a régime for the systematic employment of the potassium salt appears to be William Wallace, a surgeon in Dublin. His cases, 142 in number, were observed during the years 1832–6, and published in the *Lancet*. These lectures on the treatment of syphilis are extraordinarily interesting, are replete with sound clinical understanding and are most logically expressed. For the late venereal ulcer he advises 30 grains of potassium iodide in plenty of water, with or without the addition of syrup, to be given daily in three doses until the urine reacts very strongly and to be continued if no complications arise. Patients must show an increase of appetite and a feeling of well-being. The drug is most suitable in those cases which do not tolerate mercury well. He describes the ordinary features of iodism, and notes two cases corresponding to iodine cachexia in which emaciation, trembling, sleeplessness, and other signs (of hyperthyroidism) became apparent.

Ricord (5), hearing of Wallace's work, soon carried out his principles in France, and his widespread reputation has perhaps obscured the pride of place to which Wallace is justly entitled. No better work than that of Wallace has been noted, though Fournier, in his treatise on syphilis, somewhat elaborates it. Thereafter no important changes took place, if one excepts the occasional use of sodium iodide in place of the potassium salt, until about 1912 when, in America, a series of experiments were made with various organic compounds of iodine for oral administration. These experiments, partly carried out by McLean (6), were reviewed by him, and their results were considered inferior to those obtained by the simple inorganic salts, while Barker and Sprunt (7) more fully endorsed this view.

McLean employed (*a*) iodized proteins such as iodalbacid and iodglidin, and (*b*) iodized fats and fatty acids such as iodipin (a combination of iodine chloride and oil of sesame) and also sajodin, the calcium soap of a fatty acid obtained by iodizing erucic acid with iodo-behenic acid. His conclusions stated that they had no specific action; that they were not well utilized and must be split up to be utilized; that the second group might be helpful where the long-continued action of iodine is wanted; and that toxic side effects might arise from by-products released of the nature of fats or fatty acids.

As Barker and Sprunt's paper is the latest clinical survey, their main points are briefly summarized. No change is noted from Wallace's dosage. Potassium iodide is the most popular salt. Pure iodine is very irritating. The salts are slowly absorbed from the stomach, rapidly from the small intestine, and less so from the large bowel. Alkaline salts appear most rapidly in the secretions. Organic compounds are less rapidly absorbed and excreted. Iodism occurs more rapidly when the kidney is damaged. Iodine does not affect the general metabolism, but through the thyroid gland may produce emaciation, atrophy of mammae and testes and death.

(b) *Theories of the modes of action of iodides.* Thus Binz (8) and Heinz (9)

consider that the oxidizing property of nascent iodine, which renders the walls of the blood-vessels more permeable and stimulates a lymphocytosis, is the essential mode of action. But T. Sollmann (10) states that there is no evidence that elementary iodine can be liberated from iodide or iodate in the H-ion concentration known to exist in the body.

Or again, while Muller and Inada (11) assert that the underlying factor is a change in the viscosity of the blood caused by the iodine, Determann (12) denies any such change under the administration of iodides.

Lehndorf (13) suggests that a fall in the blood-pressure after iodide administration may be in some way accountable, but thirteen years earlier Stockman and Charteris (14) showed that no fall in the blood-pressure took place.

Much work was done by Jobling and Petersen (15), and according to them blood-serum has an antitryptic action due to the normal presence of the ferment antitrypsin. This ferment inhibiting action is said to be brought about by lipoidal combinations formed with compounds of the unsaturated fatty acids. The action of iodide is to combine with these unsaturated fatty acids, thus diminishing the antitryptic effect of serum. Then autolysis of gummatous tissue can take place with resultant absorption. It is a fact that gummatous tissues, along with cancerous, tuberculous, and suppurating tissues, show from two to three times as much iodine as is found in the corresponding healthy organs. This was found, according to Jobling and Petersen, by Loeb, Jacobi, Van den Velden, and others. Holler (16), confirming this, stated that the greatest accumulation was in tuberculous tissue.

It might here be noted that in normal tissues the highest percentage is stated to be found in the thyroid gland, lesser percentage in the blood and skin, and none in fat or bone.

Poulsson (17) and many others indicate that potassium iodide administered orally appears in the blood-stream in the form of sodium iodide and potassium chloride, and it is stated that the potassium chloride, particularly, exerts an osmotic or 'salt action' which partly explains its influence in 'promoting the absorption of morbid deposits and exudates'. All clinicians, however, note that sodium iodide given orally in a dosage equivalent to the potassium salt acts comparably upon gummata. A theoretical objection to the long-continued use of iodide is raised by Barker and Sprunt (7) who suggest that it may interfere with the natural defensive mechanisms of the body, and that cases treated with iodides always relapse, but they themselves, and indeed all clinicians, do not propose to treat syphilis by iodine alone. Further, syphilis can hardly be classed as a self-limiting or spontaneously curing disease.

The literature was then examined for more definite information concerning the fate of the iodides after their administration. Sollmann (10) states that iodide always circulates unchanged in the form of sodium iodide : that the more toxic iodate is never formed : that in H-ion concentration of the

body fluids no liberation of free iodine takes place: and that iodine given orally exists solely in the blood in the form of iodide. He considers that there should be no therapeutic difference between potassium and sodium iodide given orally.

Krahulik and Pilcher (18) investigated the relative rates of absorption and excretion of the iodides of strontium, sodium, and potassium. Strontium iodide contains the greatest percentage of iodine. They found that strontium did not delay absorption or excretion, and that the rate of absorption of iodine from strontium compounds was greatest. This difference was immaterial, and there is, therefore, no value in adopting the more unusual strontium salt.

The more exhaustive experimental work was done by Osborne (19) without, however, any clinical observations. This important paper deals with the blood concentration and urinary excretion at various times after the administration of varying quantities of sodium or potassium iodide given by the mouth, by the intravenous route or by the rectum.

Many other papers have been investigated, but nothing of material consequence was discovered.

(c) *The intravenous use of iodide in the treatment of syphilis.* Engener (20) notes great tolerance to iodide given by the intravenous route in respect of iodism, but states that thyrotoxicosis is more frequently seen. Thus he does not advocate larger doses by the intravenous route than those ordinarily given by mouth. Yet even so, selected cases may tolerate large doses by the intravenous route. Injections of NaI sometimes influence specific processes after HgKI and salvarsan have reached their highest usefulness. Further, also, the Wassermann reaction and leucoplakia of the mouth (with W. R. +) may be influenced. Also there seems to be a notable result in cases of obstinate psoriasis.

R. C. Howard (21) reports an obstinate case of laryngeal syphilis which received 125 massive doses of sodium iodide by intravenous injection, fifty-four doses of salvarsan, and many hundred intramuscular injections of mercury. The case did well.

F. J. Devota (22) records a case of tabes dorsalis which received three injections of 30 grains of sodium iodide dissolved in four ounces of normal saline. Shooting pains in the legs were relieved.

F. J. Farnell (23), (24), (25) states that ' iodides when given in the bloodstream in hypertonic form have a tendency to reduce the idiosyncrasy towards iodism '. He thinks that they aid the action of salvarsan: that they are useful in treating ' alopecia ureata and lesions referable to bone or periosteum or both '. He considers the intravenous route superior in clinical effect to the oral route. A 10 per cent. solution is used and should be freshly made.

Isacson (26) reports that, after the intravenous administration of 15 grains of sodium iodide, dermatitis, headache, nausea, and chill ensued for three days. Subsequently 2 grm. of sodium iodide orally produced no ill effect.

Various observers investigated the penetration of iodine into the cerebro-spinal fluid after different methods of administration.   Catton (27), giving potassium iodide by the mouth, found no penetration in a few cases. H. G. Mehrtens (28) was only able to detect iodine in the cerebrospinal fluid in cases of meningitis.   But Osborne (29), using a more delicate method (30), (31), (32), found traces of iodine in normal individuals in the cerebro-spinal fluid ; that the iodine content was increased after administration of iodide by oral, rectal, or intravenous route ; that the greatest concentration occurred after intravenous administration and that it could be plotted as a curve.   Neurosyphilitic tissue takes up more iodine than normal, and particularly in cases of meningitis.

Again, Cohen (33) injected 50 c.c. of 10 per cent. KI in ten cases.   At intervals of from twelve to sixty minutes cerebrospinal fluid was withdrawn and examined.   The results confirm earlier observers and do not agree with Osborne's findings (29).   The tuberculous, syphilitic, and meningococcal diseases gave positive results; other diseases, tabes, disseminated sclerosis, meningismus, and 'normals' gave negative results.

As the matter seemed contradictory, and as Kendall's method was a deli-cate one for estimating the presence of small amounts of iodine in organic material, an investigation was carried out by Professor David Campbell and the writer (34), with the objects of (a) confirming the actual facts of pene-tration or otherwise of iodine into the cerebrospinal fluid, and (b) attempt-ing to correlate any findings with the type of disease and any treatment administered.   This paper confirms the main observations made by Osborne and may be summarized by exhibiting the following table.

No. of cases.	KI or NaI administered.	Time of withdrawal of cerebrospinal fluid after admini-stration of last dose of iodide.	Mg. per 100 c.c. of cerebro-spinal fluid (average amount).
		hours.	
19	Nil	—	Nil or mere trace
12	Single dose 2–4 grm. by mouth	1	0·08
17	1·5 grm. thrice daily by mouth	1	0·38
17	1–8 grm. intravenously	½	0·08
24	1–8 grm. intravenously	1	0·28
8	10 grm. intravenously	6–7	2·03
6	10 grm. intravenously	18	0·20

This demonstrates that iodine can penetrate into the cerebrospinal fluid, that an increase can be produced and maintained by regular oral administra-tion of the simple potassium salt, and that the intravenous route may be used to increase the concentration of iodine in a marked way.

The figures given in the table represent the average of all cases, whether suffering from disease of the central nervous system or not.   To determine whether such disease had any effect on the concentration of iodine in the cerebrospinal fluid, the cases were divided into five groups: (a) Those suffering from cerebrospinal syphilis.   In this group were included not only

cases showing clinical evidence of organic changes, but also those in which the cerebrospinal fluid gave a positive reaction to the Wassermann test at least two years after a verified syphilitic infection. (*b*) Doubtful cases, in which, with an antecedent syphilitic history, there were no objective or subjective signs of disease of the central nervous system, but in which the Wassermann reaction of the cerebrospinal fluid was suspicious, or positive, within two years of the primary infection. (*c*) Those without any involvement of the central nervous system. (*d*) Cases of gross non-syphilitic nervous disease, such as spastic paraplegia, ataxic paraplegia, and disseminated sclerosis. (*e*) Normal individuals.

Comparison of the amounts of iodine in the cerebrospinal fluid in these five groups, whether iodide was given intravenously or by the mouth, showed that there was no essential difference. Disease of the central nervous system did not, in our experience, affect the passage of iodine into the spinal fluid. Our highest result, 5·5 mg. of iodine in 100 c.c., was found in a case of syphilis where there was no clinical evidence of disease of the central nervous system, and where the Wassermann reaction of the spinal fluid was negative, while the next highest was 3·8 mg. in an undoubted case of cerebrospinal syphilis. Osborne (29), in one of his cases which had marked syphilitic meningeal involvement, found as much as 42·308 mg. of iodine per 100 c.c. of spinal fluid, and, while suggesting that the meninges may be more permeable to iodine compounds when there is meningitis present, inclines to the view that tissue actively involved by syphilis takes up more iodine than normal tissue. Our clinical material was derived from an out-patient department, and accordingly we had no opportunity of making observations on any case of gross meningeal affection. Our failure to obtain any great amount of iodine in the spinal fluid of cases suffering from other forms of syphilitic disease of the central nervous system, suggests that it is damage to the meninges, rather than increased affinity of syphilitic tissue for iodine, which is responsible for rendering the cerebrospinal fluid more accessible to foreign chemical substances.

These cases have subsequently been examined to ascertain if any correlation exists between the amount of iodine present in the cerebrospinal fluid and whether or not the cases were, at that time, receiving antisyphilitic treatment with ' 914 ' and a heavy metal. No such correlation exists. In other words, the presence of small quantities of arsenic, mercury, or bismuth in the body does not influence the concentration of iodine in the cerebrospinal fluid. Sex also did not affect the results.

II. *Results of Experimental Work in 1,750 Patients*

A. *Potassium iodide by the oral route.* Solutions up to 50 per cent. in water or milk were used before and after food. Tablets were also used before and after food. It was found that the majority of cases tolerate

well any percentage strength of potassium iodide, whether water or milk be used as a solvent, and whether the mixture be given before or after food. No flavouring agent was found which either finally disguised the taste of the mixture or diminished any tendency to iodism. In a small proportion of cases the administration of potassium iodide after food produced dyspepsia lasting for an hour or so, and such cases usually complained of some degree of dyspepsia after each dose. In all cases so complaining, if the mixture was given before food the dyspepsia ceased. A number of patients objected to the taste of the watery solution with or without flavouring agents. In such cases the salt, dissolved in water, was added to half a glass of milk and taken before food. In no case did this fail to secure regular taking of the iodide. It is now a routine to give the salt dissolved in water to be taken in additional water immediately before food.

Tablets of potassium iodide were not found suitable if a single dose greater than 30 grains was desired. Dyspepsia usually followed. This could be minimized or abolished if a large quantity, a half to one pint of water was taken at the same time as the tablets.

B. *Sodium iodide by the intravenous route.* The solutions used were isotonic solutions in water, hypertonic solutions in water and normal saline respectively in dilutions from 1 per cent. to $33\frac{1}{3}$ per cent. Using isotonic aqueous solutions of NaI, experiments were carried on with a steadily increasing percentage of the aqueous solution. If the strength of solution be from 15 per cent. to $33\frac{1}{3}$ per cent., there is an advantage in that smaller quantities of fluid require to be given, and the whole operation can be carried out with one large syringe. Percentages of 15 per cent. and higher, however, frequently cause sudden and transitory severe burning pain over the deltoid region in the injected arm, with transitory flushing of the face and a feeling of vertigo. This would appear to be due to the hypertonicity of the solution, for similar complaints were found when aqueous solutions of sodium chloride of similar percentage strength were tested. Solutions of NaI of 15 per cent. or over also tend to produce thrombosis in the vein; a comparable result was found when NaCl was used. Eventually it was determined that a 10 per cent. aqueous solution was safe and painless. It is easily measured into various dosages, and easily administered by a syringe. Repeated use of the gravity method, using a needle and funnel, tends to thrombosis of the vein. No advantage accrued from using normal saline as a solvent, and it merely complicates the calculation of the percentage strengths and the consequent amount of NaI given.

C. *Sodium or potassium iodide per rectum.* The potassium salt was used in aqueous dilutions up to 20 per cent., the sodium salt up to 30 per cent. The potassium salt of iodine is not suitable for rectal administration in a watery concentration of more than 5–10 per cent. It then becomes irritating and may cause pain and diarrhoea. The sodium salt may be given in percentages up to 20 per cent. A higher percentage produces

local pain and a burning sensation.   A 10 per cent. aqueous solution is well tolerated, but must be given slowly.

A. *Reaction to dosage of oral potassium iodide.*   Idiosyncrasy occurs, and two cases have been seen in which iodism on every occasion followed a dosage varied from 2 grains to 90 grains.   No method was found of overcoming this phenomenon.   In both cases the skin showed a negative result to repeated applications of the ' patch ' test employing 5 per cent. potassium iodide as the irritant.   A number of cases showed initial intolerance, later to be referred to, but the majority of cases can tolerate, as a single oral dose, anything from $\frac{1}{48}$ of a grain to 240 grains.

In three cases 15 grains of potassium iodide thrice daily before food has been given continuously for eighteen months.   No ill effects have been noted.   Many patients have taken this dosage for six months, and to a few the taste of iodide became so obnoxious that the mixture was stopped. Such cases complained of loss of appetite.

B. *Reaction to dosage of intravenous sodium iodide.*   Idiosyncrasy was noted in one patient only.   This case could tolerate the oral administration of potassium iodide, but was unable to take half a gram of sodium iodide well diluted without iodism appearing within twelve hours.   All other cases showed no intolerance, and the only technical reasons for cessation of intravenous therapy consisted in local thrombosis or, through faulty technique, the escape of hypertonic solution into the subcutaneous tissues with resulting severe local discomfort.

The maximum single dose given was 22 grm. in 10 per cent. aqueous solution.   The daily administration of intravenous sodium iodide was only limited by the availability of the veins.   One case received 10 grm. of sodium iodide daily for three weeks with no untoward results.

C. *Reaction to dosage of combined oral and intravenous iodides.*   One patient received by the oral route 90 grains of potassium iodide four times a day, and 10 grm. of sodium iodide daily by the intravenous route for fourteen days without ill effect.

The tolerance of the average patient is thus extremely high to single oral and intravenous administration and to lengthy periods of regular dosage. Full advantage therefore can be taken of this factor in therapeutic experiments.

III.   *Intolerance to Iodides—Iodism*

The mildest grades noted were slight watering of nose or eyes or both, a slight transient or persistent erythema, usually of the face or neck.   Once only was a pustular iodide rash seen.   No cases of iodine cachexia, mild or severe, were noted.

Iodism is of common occurrence if the oral route be used.   It appeared in about 12 per cent. of those cases whose initial dose was 5 grains or less;

in about $7\frac{1}{2}$ per cent. of those whose initial dose was from 10 to 30 grains: in less than 1 per cent. if the initial dose was more than 30 grains.

Iodism usually appeared within the first week of treatment. In a number of cases where no intolerance had been noted at the outset, intolerance, while on a constant dosage, appeared at a later date. Almost all such cases had some intercurrent disease not attributable either to syphilis or iodide. Such conditions were gall-stones, cholecystitis, secondary anaemia, and pleurisy with effusion. No attempt was made in such cases to re-establish tolerance. Intolerance was thrice noted when a large dose was reduced. No other factor was determined. This was considered an exceptional and curious fact, and a number of experiments were made by the sudden reduction of dosage in the hope of inducing intolerance in other cases. All failed.

Intolerance could usually, but not always, be overcome by increasing the oral dosage—it was found that an increase to 30 grains thrice daily before food gave the best results. A smaller dosage was less reliable. The gradual increase of the dosage by 2 or 3 grains was not helpful. The administration of a large single dose of sodium iodide by the intravenous route was definitely the best way of stopping intolerance. Various quantities were tried—varying from $\frac{1}{2}$ to 16 grm. Four to 6 grm. is sufficient to stop iodism. One to 2 grm. is not. It is now a routine practice in cases of iodide intolerance to give either 4 or 6 grm. of sodium iodide by the intravenous route, and to tell the patient to continue with the oral mixture. This method and dosage has been completely successful in ninety-eight cases. It has failed once.

Apart from one patient who exhibited idiosyncrasy to intravenous sodium iodide, no case of initial intolerance to the intravenous route has been found with an initial quantity varying from a $\frac{1}{2}$ to 22 grm. If daily injections of sodium iodide be given, it is found that a small percentage of cases complain after a time of restlessness and sleeplessness. In such cases cessation of treatment led, shortly, to a return of sleep. No intolerance has been seen when injections are given at weekly intervals.

Generally it is considered that intolerance is more apt to appear in cases with greasy skins, which may or may not show seborrhoeic conditions. In three out of ten such cases showing intolerance, which were investigated, there was hyperchlorhydria. It is thought that where there is much initial sepsis, as in large infected tertiary lesions, there is an increased tendency to intolerance. Sex is not considered to influence the incidence, nor is the age of the patient. The age of the syphilitic infection has no bearing upon the incidence of intolerance. Concomitant treatment with ' 606 ', ' 914 ', mercury or bismuth is not considered to predispose to iodism. Iodide appears in the saliva, but is chiefly excreted by the kidney. Syphilitic disease of the mouth or of the kidney, and cystitis (non-syphilitic) did not appear to increase the incidence of iodism.

IV.   *The Effect of Iodide upon T. pallidum and the Primary Chancre*

Local applications of sodium or potassium iodide temporarily decreases the number of *T. pallidum*, but only if hypertonic solutions be employed. Hypertonic saline has a similar action.

In vitro T. pallidum is destroyed by all hypertonic solutions : it is not materially affected by isotonic solutions of sodium or potassium iodide.

Oral, intravenous, and rectal administration carried out singly, and in the case of oral and intravenous routes by combination, for periods of one to three days, did not reduce materially the number or the mobility of *T. pallidum*.

Boinet, in his book ' Iodotherapie ', recounts that the prolonged administration of oral iodide leads to the earlier resolution of the chancre, but not to an inhibition of secondary phenomena.

No period of treatment with iodide alone extended beyond three days. No change in the ulcer or in its secondary infection was noted in that time with any of the methods of administration described.

V.   *The Effect of Iodide upon the Secondary Manifestations*

No experiment was continued longer than one week.   This was considered advisable in the interests of the patient.   The conclusions, therefore, are only of short range, and appear as chiefly negative results.

No method of administration altered the *Treponema* content of moist lesions, except the local application of hypertonic solution.   Here too sodium chloride in hypertonic aqueous solution was equally efficacious.

No effect was seen in one week upon the resolution of moist lesions, the involution of rashes or the resolution of adenitis.   Very large doses were given by the oral route ; 120 grains four-hourly, and by the intravenous route, 10 grm. daily.

Some effect was produced upon the persistence of pigmentation in secondary syphilis.   An individual lesion, other than simple roseolar spots, shows three stages in its life history.   There is a short stage of efflorescence, lasting from three to seven days, a longer stage of florescence lasting from seven to about thirty days, and a still longer stage of deflorescence lasting from fourteen days to several months.   The deeper the lesion is situated in the skin, or the more the lesion protrudes, as in large flat papular rashes, the longer the process takes.   Further, the longer the process the longer will pigmentation persist, particularly in deep skin lesions, and definite staining has been seen eighteen months after the onset of the lesion.

The administration of ' 914 ', or ' 914 ' and a heavy metal, alters the normal course of events.   It aborts efflorescence, and any rash spots not fully out quickly disappear.   Allowance must be made for the Jarisch Herxheimer reaction.   It cuts short the stages of florescence and deflores-

cence, but it seems to have less effect upon the prolongation of pigmentary changes. The nature of this pigmentation is not known. Professor J. S. Young examined sections from a case and showed that it was not due to iron deposition from haemoglobin, nor due to mercury. In any case the pigmentation is chemically indistinguishable from that of an untreated patient in whom natural resolution occurs. If, however, the oral administration of potassium iodide be maintained throughout the first course of antisyphilitic treatment, there is no doubt, clinically, but that the production of pigmentation is diminished. An attempt was made to follow out the end result of such cases, but the numbers of apparently cured and relapsed cases do not show any significant factor. The available evidence could not be construed into the suggestion that the administration of iodide aided, through its resolvent action, the more thorough destruction of skin deposits of spirochaetes by facilitating the action of ' 914 ' or a heavy metal.

VI.   *The Action of Iodide on Tertiary Skin and Subcutaneous Manifestations*

Oral potassium iodide. Most attention has been given to this method of administration, for it is obvious that the intravenous route will only be employed by clinics and a few specialists. Certain factors were shown to have no effect in hastening or retarding resolution of all skin lesions. These were the sex of the patient, the age of the patient, the state of general health of the patient, and the occupation. Occupation is specially noted, for quite a number of tertiary lesions appear in the neighbourhood of body sites subjected to the trauma of work, e.g. rash on the outer side of thigh—lamplighter; front of thigh—shoemaker; prepatellar region—charwomen; shoulder—gamekeeper. Chronic alcoholism does not delay resolution.

A varicose condition of the adjacent veins always delayed resolution: indeed, several ulcers in the lower third of the legs required months of dressing and treatment of various kinds.

The site of the lesion was of little importance, though those lesions in regions where there was a good deal of loose subcutaneous tissue seemed to show slightly quicker resolution, and generally the more vascular parts show quicker resolution. The size of the lesion was naturally of the greatest importance, and in many cases the size is an expression of the duration of the lesion. The duration of the lesion, apart from the increase in its natural growth (or a size factor), did not affect the time of resolution. Multiple lesions behaved as did similar single lesions of corresponding type. In a few cases only the lesions, when first seen, had commenced spontaneous resolution—such showed no differences from the response to treatment of fully active conditions.

Subcutaneous gummata, with unbroken skin, disappeared most quickly of all types of lesions. Then came the nodular rashes (the tuberose syphilide), provided, also, that the skin was unbroken. Next in order of rapidity of resolution were rashes in which the hyperplastic element was reduced to a

minimum, such as those of a psoriaform type : then skin rashes, in which superficial ulceration had appeared, where, though the unbroken skin element quickly resolved, the ulcerated portions were often slow to heal. Large chronic infected syphilitic ulcers, especially if varicosity indicated poor circulation, definitely took the longest time to resolve and to heal. There were also seen in this slowly-healing group a number of osseous gummata. In one male case, where thirty-five tumours were felt on the long flat bones, three months of iodide treatment failed to make any impression. In this case X-ray examination, histological examination, serological tests, and a conjugal infection confirmed the diagnosis of syphilis.

Some curious cases of individual resistance or lack of response to iodide were seen. These were all noted while using a dosage of less than 15 gr. thrice daily, and such cases usually responded normally to an increase in the dose. In four cases the dose of iodide was not increased, but the patient was given 5 gr. of thyroid extract twice daily. Three weeks of this treatment produced no acceleration in the rate of resolution. In one case an eighth of a grain of parathyroid extract combined with 5 gr. of potassium iodide thrice daily, failed to accelerate the process of resolution in two weeks. In every case in which it was tried, the interpolation of a single intravenous injection of 4, 6, or 8 grm. of sodium iodide produced a temporary increase in the rate of resolution. This was considered to have passed off in one week. These observations led to a series of experiments with single doses of potassium iodide, varying from 1 to 240 gr., given orally. From this it was concluded that iodide exerts a rough quantitative action, but does not initiate a healing process which can then continue spontaneously. This action of the single dose of iodide was considered to increase proportionately, while the dose was raised from 1 to 30 gr. Thereafter little accrued benefit seemed to be derived from larger single doses. These observations were considered of great importance in reaching a decision as to the optimum dosage. It appears likely that, if a single dose of 120 gr., given orally, is no better than one of 30 gr., repeated dosage of the larger quantities will also fail to show increased benefit, and such is, in fact, the conclusion drawn from the various experiments with the regularly repeated administration of various quantities of potassium iodide. These observations cannot give an answer to the question of the mode of action of the iodides, but at least they do not conflict with the hypothesis expressed by Jobling and Petersen (15).
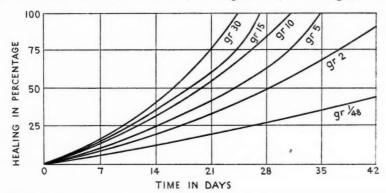
The regular administration of various quantities of iodide was then experimented with. The dose was given in water thrice daily before food. Out-patients cannot be trusted to take any medicine more frequently than this, and indeed in many cases considerable doubt existed as to whether the prescribed dose was properly taken.

The following quantities were tried :—gr. $\frac{1}{48}$, gr. $\frac{1}{24}$, gr. 1, gr. 2, gr. 3, gr. 5, gr. $7\frac{1}{2}$, gr. 10, gr. 15, gr. 20, gr. 25, gr. 30, gr. 45, gr. 60, gr. 90.

It is curious that such a small quantity as $\frac{1}{48}$ of a grain taken thrice daily should produce resolution of gummata. It was tried in five cases, and

in four, where there was no sepsis, improvement slowly and steadily took place over periods of from three to six weeks. The rate of resolution appeared to increase with each increase in dosage up to 15 gr. Thereafter it was considered that only a slight additional benefit was obtained with dosage of 20 or 30 gr. and that none was seen in the higher percentages.

It should here be noted that in visceral syphilis, particularly if there be gummatous involvement of the liver, the larger doses, 45 to 90 gr., are con-

sidered helpful. One lascar, with hepatitis, showed no clinical improvement on a dosage of 20 gr. six-hourly, but quickly improved on 60 gr. every four hours.

It is difficult to make accurate statistical comparisons of these various dosages, for the size of the lesion and the amount of secondary infection are confusing factors. Also the definition of 'resolution' is not easy. It was considered to indicate a condition wherein the underlying tissue, at the site of the lesion, could not be differentiated from healthy tissue by palpation, but, even here, allowance had to be made for scar tissue.

An attempt is made to exhibit the comparative results in the form of a rough graph in which the ordinates represent time in days, and the abscissae degrees of resolution in percentages from zero to the completed stage.

Certain abnormal cases, cases with varicose ulcers, and grossly septic cases are not included. In many cases '914' and heavy metal were given before complete resolution occurred. These curves thus have been compiled in the face of known errors, but nevertheless represent a reasonably accurate result of the comparative values of the different quantities of potassium iodide. Such errors as do occur are spread fairly uniformly throughout the series. The conclusion seems obvious—and has been already stated by William Wallace in his original paper—that the optimum dose is 15 to 30 gr. of potassium iodide given thrice daily. Further, in view of the observations noted that a single dose of potassium iodide had a quantitative effect on resolution, and that no increase in this effect was seen though the dose was increased beyond 30 gr., it seemed improbable that further experimentation

could modify this conclusion. Also, since 15 gr. thrice daily was practically
equivalent to 30 gr. thrice daily in the rate at which it produced resolution,
it was considered advantageous to employ the smaller dosage. An attempt
was then made to determine whether the repetition of the dose was neces-
sary, or whether the single daily administration of a single dose of 15 gr.
could be considered adequate. It was found that definitely better results
were achieved when the dose was repeated three times. This seems to agree
with Osborne's observation that the highest urinary concentration is noted
at from two to four hours after a dose of any quantity. Thus a repetition
of the iodide became advisable. In view of this observation, five cases
received 15 gr. of potassium iodide every two hours, day and night. All
responded well, but no acceleration was seen in the rate of absorption as
compared with those cases receiving 15 gr. thrice daily. So far, then,
clinical observation suggests quite definitely that there is no advantage in
increasing the iodine concentration of the blood-serum beyond the point
reached by 15 or 30 gr., and no advantage in reaching this concentration
more frequently than three times in the twenty-four hours. But there is
one disturbing observation already recorded, namely, that in any case the
interpolation of a single intravenous injection of 4, 6, or 8 grm. of sodium
iodide appeared, temporarily, to hasten resolution. Accordingly, a number
of cases taking 15 gr. of potassium iodide thrice daily were given a single
oral dose of 90 or 120 or 240 gr. Here, too, this interpolation of the single
large oral dose seemed to produce acceleration of resolution for a short time.
It is to be noted that, as described, the continued administration of the larger
doses did not yield corresponding benefit. Since the optimum dosage
appeared to be 15 or 30 gr. thrice daily, the temporary value of the single
large dose can be restricted to those few cases in which unfavourable factors,
already noted, are present. Therefore, where the maximum iodide effect is
wanted, a single injection of 4 or 6 grm. of 10 per cent. aqueous solution of
sodium iodide is given, combined with the oral administration of 15 gr. of
potassium iodide, thrice daily, before food. The daily injection of intra-
venous iodide, combined with the oral administration of potassium iodide,
did not appear to offer any further improvement.

  2. *Intravenous sodium iodide.* It has been explained that tolerance is
high, and a 10 per cent. aqueous solution is safe and easy to give. The
effect of potassium iodide by the mouth has just been described. Therefore,
although the earliest experiments with intravenous administration were
made independently of the oral use of the potassium salt, it was soon
realized that the difficulties of administration demanded a definite superiority
for the method if any practical result was to be achieved. The general con-
clusions just described in connexion with oral potassium iodide, as to the
factors which influence the resolution of gummatous lesions, were reached in
the case of the intravenous route, when sodium iodide was employed. In
this case, however, only forty-seven cases were utilized for experimentation,
while in the case of potassium iodide by mouth, 743 cases were experimented

on. These general conclusions, therefore, have not such a mass of experimental proof.

The quantities used were 1, 2, 3, 4, 6, 8, and 10 grm., at weekly and daily intervals. It was concluded that the weekly injection of any dose of sodium iodide was inferior to the repeated oral administration of 15 gr. of potassium iodide. It was thought that the greatest amount of clinical benefit was seen when a dosage of 6, or possibly 8 grm. was given. The daily administration of an injection of sodium iodide yielded good results, and there seemed, in these cases, no increased benefit from giving a quantity larger than 4 or 6 grm. Yet the results were in no way superior to the oral route of administration, and the technical difficulties much greater. Osborne (19) indicates that there is no difference in the rate of elimination whether the oral or intravenous route be used, or whether a large or a small dose be given. A daily injection of 4 grm. is equivalent in clinical effect to 15 gr. given thrice daily by the oral route. It is suggested on the basis of these clinical studies, that the value of iodide in a case of syphilis is concerned with the fact that a regular oral dose produces a regularly repeated rise in the iodide content of the blood-serum. No experiments have been made giving several injections of sodium iodide during the course of twenty-four hours—no theoretical advantage could appear to accrue therewith in view of the rapid rise in the blood-serum content, which Osborne states follows the use of potassium salt by mouth.

During the course of these experiments the question was raised as to whether the fact that the solutions were hypertonic had any bearing on the results—accordingly 90 or 100 c.c. of 15 per cent. aqueous solution of sodium chloride were given on three successive days to four patients, each of whom showed a tertiary skin lesion with no ulcerated areas. The curious fact was brought out that, at the end of a week, a slight degree of clinical improvement was noted in each patient. This was definitely less than was to be expected had sodium iodide been used; still each case, when first seen, had not commenced any retrograde changes. No further experiments were made along these lines, for the changes, though interesting, did not appear to be of therapeutic importance.

3. *Combined oral and intravenous iodides.* The outcome of these combined methods has necessarily been indicated in the discussion on the oral use of potassium iodide. It is to the effect that a weekly injection of 4, 6, or 8 grm. acts as a temporary adjuvant to the regular oral administration of 15 gr. thrice daily. No increased benefit followed the use of a larger quantity by the intravenous route.

4. *Rectal administration.* 1, 5, 10, and 12 grm. of sodium iodide in 10 per cent. aqueous solution were employed daily or at weekly intervals. This method of administration is not necessary. Therapeutic results are, however, achieved, and the maximum benefit seemed to be obtained from the daily employment of 10 or 12 grm. Rectal irritation was complained of after one week, in one case receiving a daily injection of 10 grm. in

10 per cent. aqueous solution.   Only twelve cases were used for this variety of experiment.

Therefore, in the treatment of tertiary muco-cutaneous lesions, it is suggested that 15 gr. of potassium iodide, well diluted in water, should be given thrice daily before food.   If intolerance to iodine is met with, give an intravenous injection of 4 grm. of 10 per cent. aqueous solution of sodium iodide, and continue the use of the oral potassium iodide.   If resolution appears unduly delayed give, at weekly intervals, an injection of 6 or 8 grm. of 10 per cent. aqueous solution of sodium iodide, and continue to employ the potassium salt by mouth in 15 gr. doses thrice daily.

These conclusions were reached by experimentation with iodide, unaccompanied by either '914' or a heavy metal.   In subsequent cases antisyphilitic treatment was employed, using '914' and Hg or Bi.   Undoubtedly lesions heal very much more quickly under the combined influence of all these drugs, but a variation of the quantities of potassium iodide, maintaining the usual course of treatment with '914' and Hg or Bi, did not lead to any different conclusions.   Conclusions were difficult to draw concerning the value of iodide in conjunction with these other drugs, as the other drugs themselves exert such a rapid and powerful effect upon tertiary skin lesions.

VII.   *The Effect of Iodide upon Certain other Tertiary Symptoms and Signs*

Pain, sleeplessness, anaemia, and loss of appetite were all relieved quickly by the use of iodide alone.   Even two grains of potassium iodide, thrice daily, alleviated the night pains of syphilitic periostitis of the tibia.   In three weeks' time, giving 15 gr. of potassium iodide thrice daily before food, and no other therapy, in one case the haemoglobin rose from 65 to 83 per cent. and the R.B. cells from 4,100,000 to 4,580,000.   An increased sense of well-being was almost universally experienced by all cases.

VIII.   *The Effect of Iodide in Latent Syphilis*

Latent syphilis is defined as a condition in which the Wassermann reaction of the blood-serum is positive, in which no clinical signs of syphilis are found, and in which, if a definite history of primary or secondary infection be obtained, it is of at least two years' duration.

Three cases received 15 gr. of potassium iodide, thrice daily, for eighteen months.   No clinical relapse occurred: no alteration from a positive blood Wassermann was noted.

The continuation of 15 gr. of potassium iodide, thrice daily, throughout the whole periods when '914' and metal (Hg or Bi) were given did not lead to a greater percentage of final favourable serological results.   This cannot be considered as a properly controlled statement, for although many cases did not receive iodide along with other drugs, small quantities of intercurrent iodide therapy were given to almost every case.

The use of intravenous sodium iodide was not made in a systematic manner, and a table showing the actual quantities given to all these cases, male or female, treated and observed for more than two years, is therefore subjoined.

The cases are subdivided according to whether the total treatment given could be termed adequate or inadequate and whether the final serological result was negative (satisfactory) or not negative (unsatisfactory). The amount of sodium iodide is shown in grams.

NaI in Latent Syphilis observed for Two Years or Longer

Total amount of intravenous NaI in grm.

Treatment.	Result.	0.	1–20.	21–50.	51–75.	76–100.	More than 100.
Adequate	Satisfactory	35	2	5	3	0	1
Inadequate	Satisfactory	6	0	0	0	0	0
Adequate	Unsatisfactory	29	4	6	5	2	1
Inadequate	Unsatisfactory	5	1	0	1	0	0

No definite conclusions of value can be drawn from this table. The increase in the numbers of cases getting intravenous sodium iodide, which, after receiving adequate treatment, finally showed an unsatisfactory serological result is possibly due to attempts to reverse the positive Wassermann reaction by all available methods of therapy. It is, however, suggested that this indicates that intravenous sodium iodide is not of much benefit in securing a final negative serological result in latent syphilis.

IX. *The Effect of Iodide upon the Wassermann Reaction of the Blood-serum*

A. *In early syphilis.* After 1923, i.e. after the replacement by bismuth of mercury as the heavy metal to be given concomitantly with ' 914 ', the standard course in early syphilis consisted of ten injections of ' 914 ', equivalent to 5·85 grm., and twelve intramuscular injections of bismuth metal, equivalent to 2·4 grm. of metal. Normally potassium iodide was given in a dose of 15 gr., thrice daily, for three weeks during a rest period between the eighth and tenth weeks. It was considered theoretically possible that the continued administration of potassium iodide throughout the whole course might be of advantage. This view was based on the known action of iodide on gummatous tissue. It was thought that the continued use of iodide might prevent the formation of gummatous deposits in the tissues, and, by facilitating the access of antisyphilitic drugs, lessen the tendency to late serological and clinical relapse. Should this prove the case the therapeutic value of such a proceeding would be obvious. A careful search through the literature failed to bring out any comparable experiment. Such an experiment requires much time to enable any definite conclusions to be drawn, and it is felt that at least five years' observation is necessary. Only a few cases have remained under observation for such a period, and therefore statistical evidence is scanty. This answer is quite inconclusive, since almost all cases

observed for such a time did well, whether the treatment consisted of '914' and Hg or of '914' and Bi, or of '914' and Bi and KI.

An analysis of those cases which had been under observation for two years was then made. At the end of this period a preliminary attempt is always made to determine whether or not a case can be termed 'cured', and if it be thought 'cured' no further treatment is given. There was a very slight improvement in the percentage of satisfactory serological end results in early syphilis, male and female, when iodide was used continuously with '914' and Bi. This was noted as compared with those cases in which '914' and Bi only were employed, and also in comparison with the cases treated with '914' and Hg. It is not considered to be a significant figure, because, firstly, the numbers are small; and, secondly, these cases, on the whole, have tended to receive more complete courses of '914' and metal since they occurred in the later years.

Finally, the cases were analysed in an attempt to ascertain if the continuous use of iodide throughout the first course of treatment produced a greater percentage of negative serological results at the end of this first course. No such improvement was found.

It can be definitely stated that the continuous use of iodide does not increase the incidence or the severity of arsenical, mercury, or bismuth intolerance in this series of cases.

It is concluded that the continuous use of iodide throughout treatment with '914' and a heavy metal is not shown to be of value either in the production of a negative serological test at the end of the first course, at the end of two years, or at the end of five years.

A number of cases of early syphilis on completion of their standard treatment, and on attaining a repeatedly negative Wassermann reaction of the blood, were given a series of intravenous injections of sodium iodide at weekly intervals with the idea of thus aiding in the maintenance of a 'cured' condition by preventing any gummatous tissue formation. Twenty-four cases were so treated, receiving from 27 to 104 grm. of NaI. All cases did well, but no deduction is made therefrom.

B. *In late and congenital syphilis.* No Wassermann improvement followed the administration by mouth of 15 gr. of potassium iodide thrice daily, for periods of twelve to fifteen months in eleven cases of tertiary syphilis—nor for periods of eight to twelve months in thirty-seven cases. In one case the Wassermann reaction of the blood-serum changed from positive to negative after nine months, during which nothing but potassium iodide was given. It shortly relapsed again to positive. Hundreds of cases received potassium iodide for periods of three to four months without any serological change, except in a small percentage (1·6 per cent.). Such favourable changes were only temporary, and can easily be attributed to the antecedent antisyphilitic treatment which they had received. The percentage of such favourable changes did not differ from that seen after rest periods of comparable length, during which no treatment was administered.

An extensive series of experiments was made employing intravenous sodium iodide at weekly intervals, both in conjunction with antisyphilitic drugs and as the sole intercurrent treatment.   Male and female cases, with various skin and subcutaneous lesions of late syphilis, with neurosyphilis and with congenital syphilis were treated.   The Wassermann reaction of the blood-serum was ascertained shortly after the completion of a ' course' of treatment.   The results were then analysed in respect of the factors above mentioned, and also the amount of NaI given in grams.   Quantities were grouped in three categories, less than 100 grm., less than 150 grm., more than 150 grm.   Two hundred and ninety-two cases were investigated.   In the cases with tertiary skin and subcutaneous or congenital lesions, the number of favourable changes in the Wassermann reaction of the blood-serum, when NaI was used, shows a higher percentage than in an equivalent series of cases treated without NaI.   The difference was very slight and not considered significant.

The serological improvement was only temporary, and did not seem to affect the final outcome of the case to any great extent; and as the final serological result is not materially affected, there seems no need to introduce this method of therapy during the earlier stages of treatment.

With respect to the cases of neurosyphilis, a similar temporary improvement is noted in the immediate Wassermann reactions.   It should be pointed out, however, that the serological reactions of the blood and cerebrospinal fluid are not considered of such prognostic importance in neuro- and cardiovascular syphilis as in the other late manifestations of syphilitic disease.

Many cases of neurosyphilis progress clinically in spite of negative serological tests.   Therefore, in connexion with the use of intravenous sodium iodide, the question of clinical benefit has to be noted.   It is definitely thought that its employment is followed by an increased feeling of well-being in a considerable proportion of cases, and that many subjective phenomena are temporarily improved.   Improvement has been noted in respect of the cessation of pain, ability to walk, less inco-ordination, tremor, and clearer speech.   The best results are obtained when ' 914 ' is given concurrently. It is thought that sodium iodide may advantageously be used at some stage or another in the treatment of most cases of neurosyphilis, but it should not be employed in the earlier stages for fear of setting up the Jarisch Herxheimer reaction.

A further series of experiments was made with the use of hypertonic aqueous solutions of sodium iodide in order to facilitate the entrance of arsenic into the cerebrospinal fluid.

Spinal drainage has been employed in an attempt to increase the penetration of drugs, such as salvarsan, into the cerebrospinal fluid, and thereby to enhance its therapeutic effect in the treatment of neurosyphilis.   Thus Gilpin and Early (35) in 1916, after the administration of arsphenamin by the intravenous route, later removed by lumbar puncture a quantity of cerebrospinal fluid.   They reported satisfactory clinical results.   For patients

attending clinics it is not always possible to secure in-patient accommodation, and some substitute for lumbar puncture is desirable.

A method was suggested by Corbus, O'Connor *et al.* (36) in 1928. This consisted in the administration of 100 c.c. of 15 per cent. aqueous solution of sodium chloride by intravenous injection six hours before the administration of neo-arsphenamin. The *rationale* of this procedure is derived from a study of the following points.

Weed and McKibben (37), in 1919, showed that the intravenous injection of hypertonic saline solution caused an initial rise in the pressure of the cerebrospinal fluid, and a subsequent fall, often to zero. Foley and Putnam (38) confirmed this. Foley (39) states that this fall in pressure disturbs the normal circulation of the cerebrospinal fluid so much that intraventricular absorption of fluid occurs through the choroid plexuses and ependyma. Presumably this is a result of an effort to maintain the blood-serum at its normal specific gravity. Restoration of the spinal fluid begins about the sixth hour after injection of the hypertonic saline and the normal pressure is restored one to three hours later. If, then, salvarsan be given about the sixth hour, there should be a greater degree of absorption of arsenic from the blood-stream than ordinarily occurs.

Corbus found in the treatment of thirty patients that arsenic did penetrate into the cerebrospinal fluid in twenty-eight cases, and that, clinically and serologically, the results of this method were encouraging.

In the course of investigations conducted with Professor David Campbell (34) on the penetration of iodine into the cerebrospinal fluid, it was found that, if sodium iodide was given in aqueous solution either orally or by the intravenous route, penetration did occur into the cerebrospinal fluid. The degree of concentration in the cerebrospinal fluid was not parallel with that of the blood-stream in which case concentration is greatest at an early time. In the cerebrospinal fluid the iodine concentration was definitely higher six hours after injection, than it was a half, one or two hours after administration.

With these facts in mind an attempt was made to perform drainage without lumbar puncture, using the principle set out by Corbus, but employing a hypertonic solution of sodium iodide in place of the simple saline. The technique was as follows : At 11.30 a.m. each patient received, by intravenous injection, 100 c.c. of distilled water containing 10 grm. of sodium iodide and 5 grm. of sodium chloride to increase the hypertonic effect. Patients were then sent home, preferably to bed. They returned at 5.30 p.m. for an intravenous injection of neokharsivan, usually 0·6 grm., and thereafter were again sent home to bed with instructions to stay there for twenty-four hours in any case, or forty-eight hours if malaise, headache, or fever appeared. No case required to spend more than twenty-four hours in bed.

The results of treatment are set out in the following table. Six cases, all male, were investigated.

Case no.	Clinical condition.	Previous treatment with salvarsan substitute.	Wassermann reaction before treatment.		No. of injections of N.K. and NaI.	Wassermann reaction after treatment.	
			Bd.	C.S.F.		Bd.	C.S.F.
1,186	Advanced tabes	Yes	+	+	8	S	+W
1,808	Ataxia para-plegia	Mercurial only	S	+	7	—	+
1,891	Spastic para-plegia	Yes	—	S	9	—	—
2,072	Tabes with 3rd nerve involve-ment	Mercurial only	+	+	8	+W	S
2,189	Cerebrospinal syphilis with mental impair-ment	No treatment	+	+	8	+	—
2,166	Latent syphilis-asthma	Mercurial only	+	—	4	0	0

Clinical improvement took place in the first five cases. Treatment was stopped in No. 2,166 owing to the persistent severity of his asthma. It had been hoped that the iodide might have helped the asthmatic condition. It is quite noteworthy that in each completed case some serological improvement took place and, with the exception of No. 1,808, it was the first favourable change recorded.

No. 2,072 developed jaundice immediately after his eighth injection. He was admitted as an in-patient. The jaundice ran a mild course and, under treatment, completely disappeared in five weeks.

These cases have been kept under observation for over a year. The improvement, both clinical and serological, was only of a temporary nature as was to be expected, having regard to the clinical condition. In all cases further treatment with antisyphilitic remedies was continued.

In view of the fact that a definite, though temporary, improvement took place in the serological reactions, and that this was accompanied by clinical improvement, it is suggested that this method deserves a trial in selected cases. The serological improvement is noteworthy, since one would not anticipate any change of this nature after so short a course of treatment in advanced neurosyphilis.

Conclusions

The results of experiments on 1,750 cases are given and show :—

(1) Iodides have no effect upon the spirochaete content of the lesions in primary or secondary syphilis.

(2) Iodides cause the resolution of tertiary skin lesions. The optimum dosage is 15 grains thrice daily. The interpolation of a single oral dose of 120 grains of potassium iodide or the intravenous dose of 6 grm. of sodium iodide temporarily accelerates resolution in refractory cases.

(3) The exhibition of iodide does not lead to increased intolerance to other measures of antisyphilitic treatment.

(4) Iodism can be stopped by the intravenous administration of 4 grm. of sodium iodide.

(5) Iodides have no effect on the Wassermann reaction in any stage of syphilitic infection and play only a minor part in antisyphilitic treatment.

REFERENCES

1. Coster, J., *Arch. gén. de Med.*, Paris, 1823, 11.
2. Brera, *Saggio clin. sull'idio, &c.*, Padova, 1822 (quoted by Coster).
3. Boinet, A. A., *Iodothérapie*, 1855.
4. Buisson, *Thèses de la Fac. de Paris*, 1825, No. 223 (quoted by Boinet).
4a. Wallace, W., *Lancet*, Lond. 1836, 2.
5. Ricord, *Bull. de Thérap.*, 1837, xii. 241.
6. McLean, F. C., *Arch. Int. Med.*, Chicago, 1915, xv. 92.
7. Barker, L. F., and Sprunt, T. P., *Therap. Gaz.*, Detroit, 1922, N.S. xxviii. 539.
8. Binz, C., *Arch. f. exper. Path. u. Pharm.*, Leipz., 1894, xxxiv. 185.
9. Heinz, R., *Virchow's Arch. f. Path. Anat.*, Berl., 1899, clv. 44.
10. Sollmann, T., *Journ. Pharm. and Exper. Therap.*, Balt., 1917, ix. 269.
11. Muller, O., and Inada, R., *Deutsch med. Wchnschr.*, Leipz., 1904, xxx. 1751.
12. Determann, *ibid.*, 1908, xxxiv. 871.
13. Lehndorf, A., *Arch. f. exper. Path. u. Pharm.*, Leipz. and Berl., 1914, lxxvi. 224.
14. Stockman, R., and Charteris, F., *Brit. Med. Journ.*, Lond., 1901, ii. 1520.
15. Jobling and Petersen, *Arch. Int. Med.*, Chicago, 1911.
16. Holler, G., *Klin. Wchnschr.*, Berl., 1923, 1692.
17. Poulsson, E., *Textbook of Pharmacology and Therapeutics*, Lond., 1923, 390.
18. Krahulik, E. J., and Pilcher, J. D., *Arch. Int. Med.*, Chicago, 1918, xxi. 176.
19. Osborne, E. D., *Journ. Amer. Med. Assoc.*, Chicago, 1922, lxxix. 615.
20. Engener, *Münch. med. Wchnschr.*, 1917, lxiv. i. 760.
21. Howard, R. C., *Amer. Journ. Syph.*, St. Louis, 1918, xi. 850.
22. Devota, F. J., *Lancet*, Lond., 1919, 1. 339.
23. Farnell, F. J., *Arch. Neur. and Psych.*, Chicago, 1922, vii. 729.
24. Farnell, F. J., *Journ. Neur. and Ment. Dis.*, N. York, 1922, lv. 112.
25. Farnell, F. J., *N. York Med. Journ.*, 1923, cxviii. 290.
26. Isacson, L., *ibid.*, 1923, cxviii. 322.
27. Catton, J. H., *Journ. Amer. Med. Assoc.*, Chicago, 1916, lxvii. 1369.
28. Mehrtens, H. G., *Calif. State Journ. Med.*, San Fran., 1918, xvi. 306.
29. Osborne, E. D., *Journ. Amer. Med. Assoc.*, Chicago, 1921, lxxvi. 1384.
30. Kendall, E. C., *Journ. Amer. Chem. Soc.*, Easton Pa., 1912, xxxiv. 894–909.
31. Kendall, E. C., *Journ. Biol. Chem.*, Balt., 1914, xix. 251.
32. Kendall, E. C., *ibid.*, 1920, xliii. 149.
33. Cohen, H., *Lancet*, Lond., 1924, 1. 127.
34. Campbell, D., and Snodgrass, W. R., *Journ. Pharm. and Exper. Therap.*, Balt., 1926, xxvii. 355.
35. Gilpin, S. F., and Early, T. B., *Journ. Amer. Med. Assoc.*, Chicago, 1916, lxvi. 260.
36. Corbus, B. C., O'Connor, V. J., Lincoln, Mary C., Gardner, Stella M., *ibid.*, 1922, lxxviii. 264.
37. Weed, L. H., and McKibben, P. S., *Amer. Journ. Physiol.*, Balt., 1919, xlviii. 512.
38. Foley, F. E. B., and Putnam, T. J., *ibid.*, 1920, liii. 464.
39. Foley, F. E. B., *Surg., Gyn. and Obstet.*, Chicago, 1921, xxxiii. 126.

269

616.124
616.72–002.77

THE PLASMA PROTEINS AND NON-PROTEIN NITROGEN, AND THE SEDIMENTATION RATE, IN CHRONIC RHEUMATIC DISORDERS[1]

By G. R. P. ALDRED-BROWN and J. M. H. MUNRO
(From the Royal Mineral Water Hospital, Bath)

THE main object of this investigation was to throw light on the alleged connexion between the amount of albumin, globulin, and fibrinogen, in the blood-plasma, and their ratio to the total proteins, in chronic rheumatic disorders. To this end we have made a series of analyses forming a record of the amounts and distribution of the plasma proteins occurring in these disorders, concerning which there is little published information.

Two further objects we had in view were : (i) to call attention to the great alterations in the rate of sedimentation of the red-blood cells in the various rheumatic disorders, and (ii) to record the values of the plasma non-protein nitrogen therein.

The methods of analysis adopted we have fully described elsewhere (1), together with our results and conclusions as regards the relationship of the plasma proteins to the sedimentation rate.

We have here made a deviation from our previous method of recording the sedimentation rate. For whereas previously the fall in one hour after mixing was taken as the measure of the sedimentation rate, we now record the sedimentation rate as the height of the column of red cells expressed as a percentage of the original blood level. Thus if we record a S.R. value of 60 per cent. this obviously infers that the fall of the corpuscular mass has been 40 per cent from its original adjustment to 100 per cent. This step we have taken in order that results may be the more easily compared with other workers who have based their methods on those of Zecker and Godsell.

Against each individual case we have plotted its own value as regards the albumin, globulin, fibrinogen, and the total proteins, and the non-protein nitrogen percentages, together with the sedimentation rate.

The various cases of chronic rheumatic disorders tabulated in this paper have been diagnosed after a careful survey of the clinical, X-ray, and biochemical findings. Our nomenclature does not differ from that of the arthritis committee of the B.M.A. (1933), save that we do not divide rheumatoid arthritis into a primary group and a secondary group.

Much work has been done on the plasma protein concentrations in subjects of nephritis, with or without oedema, and in some papers 2, 3, 4, 5, observations on normal controls have been included. Whilst many of the workers agree in the main as to the average normal concentration of each individual protein, there would appear to be a wide margin between the lowest and the highest value 'ound normally.

During the course of this investigation it was realized that even allowing for such a wide normal variation, our figures for the concentrations found in chronic rheumatic disorders varied very appreciably from the figures, as published, of normal concentrations. It therefore became imperative for us to establish *our own* normal ranges and averages, since differences in technique in the analysis in our work and in that of other investigators might lead to discrepancies.

We therefore estimated the various concentrations in nine healthy men varying in age from 21 to 36 (chiefly policemen), and three healthy nurses varying in age from 18 to 26. Our results are tabulated in Table I. It will be seen that the albumin ranged from 4·00 to 5·31 with an average of 4·51. The globulin from 0·98 to 2·38 with an average of 1·69. The fibrinogen from 0·09 to 0·25 with an average of 0·16. The total proteins varied from 5·73 to 6.83 with an average of 6·37, whilst the non-protein nitrogen varied from 0·010 to 0·024 with an average of 0·017.

In order that our normal ranges and averages may be compared with those found by other investigators, the various figures are set forth in Table II, our twelve cases being placed at the head of the table. It will be seen that our figures for albumin agree with those of other workers, but both the globulin and fibrinogen have a lower range and lower average value. This presumably accounts for the fact that our average for the total proteins is slightly lower than the other reported averages. Our range and average for the non-protein nitrogen also are slightly lower.

Table III gives the data figures we have found in thirty-four cases of rheumatoid arthritis: Table IV the figures in nine cases of osteo-arthritis: Table V those in twelve cases of spondylitis ankylopoietica. Table VI gives a record of the figures found in five cases of fibrositis, four cases of subacute rheumatic infection and three cases of gout. The number of cases, however, grouped in Table VI are too small for any reasonable deductions to be drawn.

In Table VII we have given the percentages of the number of cases in Tables 3, 4, and 5 that lie outside our normal ranges as listed in Table II. The sign + denotes those that lie above the maximum normal, and the sign − denotes those below minimum normal.

There are several points worthy of comment in Table VII:

The albumin in osteo-arthritis, whilst still markedly below normal, tends to be lower still in rheumatoid arthritis and in spondylitis ankylopoietica. The fibrinogen is more increased in spondylitis ankylopoietica than in the other two conditions. There is a marked difference in the total protein content in the three disorders. In rheumatoid arthritis it is roughly three

times as much as in osteo-arthritis, whilst in spondylitis ankylopoietica it is nearly twice as much as in rheumatoid arthritis.   In the former case the difference would appear to be chiefly made up of the difference in albumin percentage, whereas in the latter the difference would appear to be accounted for by the increase in globulin percentage.   A comparison of the average values for the total proteins shows that whereas in spondylitis ankylopoietica there is a deviation from the normal, in rheumatoid arthritis and osteo-arthritis the values are coincident with the normal.

But do our normal data figures *really* represent the population at large? For example, does Mrs. A., aged 45, a housewife, who is suffering from rheumatoid arthritis, have materially different values as regards her plasma protein concentrations, &c., from Mrs. B., of similar age, subjected possibly to similar strains and stresses of economic and married life, who has never yet had the slightest twinge of rheumatism?

This is a point that is often neglected when the question of normal values are compared with the values obtained in diseased persons.   To assume that values found in healthy young adults are similar to the values found in elderly persons, even though the latter be without any ascertainable disease process, must at times, of necessity, lead to erroneous conclusions.

Accordingly, we secured the services of eighteen men and women volunteers from the local branch of the British Legion.   The Legion would have willingly supplied us with ten times that number, but our firm criterion was that no one of the volunteers should have ever at any time ' felt a twinge of rheumatism '.
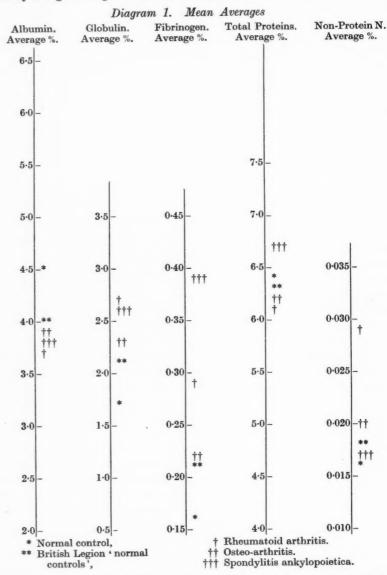
Table VIII shows in the data figures obtained in these eighteen cases, nine men and nine women.   Their ages ranged from 18 to 64, the average age being approximately 40.

In Table IX are given the percentages of the number of cases in Tables III, IV, and V, that lie outside the maximal and minimal values found in the British Legion ' normal controls ' as listed in Table VIII.

It is illuminating to compare Table IX with Table VII.   The distinctive subminimal values in albumin have disappeared, likewise the marked super-maximal values found in the globulin, fibrinogen, total protein, and non-protein nitrogen percentages have gone.   There are, however, two notable exceptions : one is the 25 per cent. of cases of spondylitis ankylopoietica, and the other the 26 per cent. of cases of rheumatoid arthritis, both figures in excess of the maximal figures for fibrinogen and total proteins respectively as given by the British Legion ' normal controls '.

We would further call attention to the differences in the sedimentation rates in Table IX as compared to those in Table VII.   This point and others connected with the sedimentation rates tabulated here will be dealt with fully in a later paper.

We would point out that the range between maximum and minimal values in the normal controls and that found in the British Legion ' normal con-trols ' show some interesting points. First, with the exception of the albumin

percentage, complete agreement in both sets of figures as to the *minimal* values found in the other percentages. Secondly, it appears that with increasing age, work, or unemployment, as the case may be, poverty or possibly hunger—in general, the strains and stresses of life—the plasma

Diagram 1. Mean Averages

| Albumin. Average %. | Globulin. Average %. | Fibrinogen. Average %. | Total Proteins. Average %. | Non-Protein N. Average %. |

* Normal control,
** British Legion 'normal controls',
† Rheumatoid arthritis.
†† Osteo-arthritis.
††† Spondylitis ankylopoietica.

protein percentages of those persons subjected to the above conditions, although free from rheumatism, tend to approach closely the figures obtained from those suffering from chronic rheumatic disorders.

In Diagram 1 are shown the *average* values found in rheumatoid arthritis, osteo-arthritis, and spondylitis ankylopoietica, together with the *average* values in the normal controls and the British Legion 'normal controls'. This diagram further bears out our contention that the average values for the British Legion 'normal controls', or the population from which our cases of chronic rheumatic disorders are drawn, tend to approximate to the values found in the subjects of chronic rheumatic disorders. It further illustrates how osteo-arthritis deviates the least from normal; that spondylitis ankylopoietica has a high value of fibrinogen, with rheumatoid arthritis occupying a position midway between it and osteo-arthritis: that spondylitis ankylopoietica tends to have a higher total protein value; whilst lastly, it illustrates the high non-protein nitrogen percentage found in rheumatoid arthritis.

Conclusions

1. There are wide variations in the values of the proteins, the total proteins, and the non-protein nitrogen between individuals in each of the three groups investigated, viz. (A) healthy young adults, (B) subjects suffering from chronic rheumatic disorders, and (C) non-rheumatic persons whose ages and economic stresses resemble the preceding group of chronic rheumatics.

2. Group B has a large percentage of cases with an albumin value *below the minimum* value found in Group A, whereas as regards globulin, fibrinogen, total proteins, and non-protein nitrogen, Group B has a large percentage of cases *above the maximal* values found in Group A.

3. The range of values found in Group B and Group C resembles one another fairly closely. From this it is inferred that several factors, of which possibly increasing age and economic stress may be two, cause the plasma proteins to deviate from the values found in Group A. This too is shown by the fact that the mean averages for the individual proteins, &c., in Group C in each case deviate from the mean averages found in Group A, and approach the mean values found in Group B.

4. The mean averages of the fibrinogen percentages in spondylitis ankylopoietica and rheumatoid arthritis are high, as is also the mean average of the non-protein nitrogen percentages in rheumatoid arthritis.

TABLE I. *Normal Controls*

(12 cases, 9 males, 3 females)

Proteins % of plasma

	Age.	Albu-min.	Globu-lin.	Fibri-nogen.	Total proteins.	Non-pro-tein N.	Sedimentation rate %.
Average	24	4·51	1·69	0·16	6·37	0·017	95
Maximum	36	5·31	2·38	0·25	6·83	0·024	99
Minimum	18	4·00	0·98	0·09	5·73	0·010	90

TABLE II. *Normal Controls, Previous Authors*

	Ages.	Albu-min.	Globu-lin.	Fibri-nogen.	Total proteins.	Non-protein N.
12 Cases	18–36	4·00–5·31	0·98–2·38	0·09–0·25	5·73–6·83	0·010–0·024
(9 Males, 3 Females)		*Av. 4·51*	*Av. 1·69*	*Av. 0·16*	*Av. 6·37*	*Av. 0·017*

Salvesen (2)

16 Males	23–27	3·95–5·24	1·96–3·16	—	6·53–7·96	0·020–0·031
		Av. 4·44	*Av. 2·58*	—	*Av. 7·00*	—
16 Females	23–40	3·77–4·80	2·18–3·55	—	6·34–7·96	0·016–0·025
(42 Determinations)		*Av. 4·35*	*Av. 2·68*	—	*Av. 7·02*	*Av. 0·020*

Linder, Lunsgaard, and Van Slyke (3)

7 Cases

(Age and Sex not		3·36–4·90	2·26–2·89	—	5·62–7·45	0·014–0·030
stated)		*Av. 4·11*	*Av. 2·61*	—	*Av. 6·73*	*Av. 0·020*
(8 Determinations)						

Moore and Van Slyke (4)

9 Cases

(Age and Sex not		4·00–4·50	—	—	6·50–7·70	—
stated)		*Av. 4·30*	*Av. 2·80*	—	*Av. 7·10*	—

Thomson (5)

3 Males		4·17–4·92	2·31–2·56	—	6·73–7·49	—
		Av. 4·63	*Av. 2·56*	—	*Av. 7·11*	—

Harrison (6)

		3·40–6·70	1·20–2·90	0·20–0·38	5·80–8·60	0·018–0·030

Cameron (7), *and Hawk and Bergeim* (8)

		4·60–6·70	1·20–2·30	0·30–0·60	6·70–8·20	—

TABLE III. *Rheumatoid Arthritis*

(34 cases, 12 males, 22 females)

Proteins % of plasma

	Age.	Albu-min.	Globu-lin.	Fibri-nogen.	Total proteins.	Non-protein N.	Sedimentation rate %.
Average	41	3·70	2·62	0·29	6·32	0·029	59
Maximum	63	4·94	4·22	0·62	8·13	0·054	97
Minimum	15	2·19	1·32	0·14	5·11	0·016	36

TABLE IV. *Osteo-arthritis*

(9 cases, all males)

Proteins % of plasma

	Age.	Albu-min.	Globu-lin.	Fibri-nogen.	Total proteins.	Non-protein N.	Sedimentation rate %.
Average	62	3·91	2·32	0·22	6·35	0·020	84
Maximum	71	5·04	3·90	0·34	7·69	0·032	93
Minimum	51	2·94	0·45	0·15	5·83	0·014	67

TABLE V. *Spondylitis Ankylopoietica*

(12 cases, all males)

Proteins % of plasma

	Age.	Albu-min.	Globu-lin.	Fibri-nogen.	Total. proteins.	Non-protein N.	Sedimentation rate %.
Average	32	3·80	2·59	0·38	6·78	0·017	65
Maximum	42	4·24	3·21	0·73	7·35	0·033	85
Minimum	19	3·24	1·82	0·19	5·81	0·011	48

TABLE VI. *Fibrositis*

(5 cases, 3 males, 2 females)

Proteins % of plasma

	Age.	Albu-min.	Globu-lin.	Fibri nogen.	Total proteins.	Non-pro-tein N.	Sedimentation rate %.
Average	43	3·78	1·77	0·34	5·88	0·038	87
Maximum	65	5·12	2·73	0·63	6·50	0·074	92
Minimum	24	3·13	0·75	0·20	5·31	0·025	75

Subacute Rheumatic Infection

(4 cases, 1 male, 3 females)

Average	42	4·34	1·82	0·22	6·37	0·022	77
Maximum	63	5·94	2·62	0·27	7·94	0·025	80
Minimum	18	3·19	0·88	0·16	4·31	0·021	73

Gout

(3 cases, all males)

Average	58	4·20	2·49	0·42	7·14	0·026	71
Maximum	62	4·37	2·99	0·36	7·31	0·033	76
Minimum	49	4·04	2·21	0·28	6·94	0·021	66

TABLE VII

	Albumin.	Globulin.	Fibrinogen.	Total proteins.	Non-protein N.
Rheumatoid arthritis (34 cases)	70 % —	53 % +	50 % +	35 % +	68 % +
Osteo-arthritis (9 cases)	44 % —	55 % + 11 % —	44 % +	11 % +	22 % +
Spondylitis ankylo-poietica (12 cases)	66 % —	75 % +	58 % +	66 % +	8 % +

TABLE VIII. *British Legion Normal Controls*

(18 cases, 9 males, 9 females)

Proteins % of plasma

	Age.	Albu-min.	Globu-lin.	Fibri-nogen.	Total proteins.	Non-pro-tein N.	Sedimentation rate %.
Average	39	4·09	2·13	0·22	6·35	0·018	87
Maximum	64	4·77	4·31	0·54	7·48	0·034	97
Minimum	18	3·06	1·07	0·10	5·80	0·011	62

TABLE IX

	Albumin.	Globulin.	Fibrinogen.	Total proteins.	Non-protein N.
Rheumatoid arthritis (34 cases)	14 % —	—	3 % +	9 % + 3 % —	26 % +
Osteo-arthritis (9 cases)	11 % —	11 % —	—	11 % +	—
Spondylitis ankylo-poietica (12 cases)	—	—	25 % +	—	—

REFERENCES

1. Aldred-Brown, G. R. P., and Munro, J. M. H., Lancet, 1934, i. 1333.
2. Salvesen, H. A., *Acta Med. Scand.*, Stockholm, 1927, lxv. 147.
3. Linder, G. C., Lunsgaard, C., and Van Slyke, D. D., *Journ. Exper. Med.*, 1924, xxxix. 887.
4. Moore, N. S., and Van Slyke, D. D., *Journ. Clin. Invest.*, 1930, viii. 337.
5. Thomson, W. A. R., *Quart. Journ. Med.*, Oxford, 1934, iii. 587.
6, Harrison, G. A., *Chemical Methods in Clinical Medicine*, Lond., 1930.
7. Cameron, A. T., *A Textbook of Biochemistry*, Lond., 1929.
8. Hawk, P. B., and Bergeim, O., *Practical Physiological Chemistry*, Lond., 1931.

A COMPARISON OF VARIOUS DIETS IN THE TREATMENT OF DIABETES MELLITUS [1]

By E. M. WATSON and MARION A. WHARTON

(From the Department of Medicine, Division of Pathological Chemistry, University of Western Ontario Medical School, London, Canada)

INSULIN has enabled present-day diabetics to enjoy more liberal and more natural diets than were thought possible heretofore, and this has entailed some rather radical departures from the preconceived views concerning the allowance of carbohydrate-containing foods for patients with this disease.

The so-called higher carbohydrate diets for diabetics have received widespread but not universal approval. The fact that some students of nutrition, who through experience or conviction have not acceded to the vogue of a liberal carbohydrate allowance is an indication that the optimum type of diet for the diabetic has not been achieved as yet. Furthermore, this lack of unanimity with respect to diet therapy invites a critical scrutiny of the various dietary measures which have been advocated, with a view to comparing their relative merits from the standpoint of the most efficient treatment.

There are, of course, certain generally accepted principles which contribute to the successful management of a diabetic. For instance, it is recognized that the total caloric intake should be such as to maintain the body weight slightly below that which is regarded as normal for the individual. The protein content of the diet should be adequate but not high. The blood-sugar should be maintained, if possible, within the normal limits and the urine kept free of sugar and ketones. The most satisfactory way of accomplishing these criteria and at the same time keeping the patient contented has been a subject for controversy, mainly with regard to the relative amounts of fat and carbohydrate allowable. While some of the dietary procedures are radically opposed to one another, they all seem to be meritorious according to the opinions of their advocates, and it is a rather paradoxical situation that confronts the inquirer.

The dietary measures concerning which there has existed the greatest degree of controversy are: (1) the low carbohydrate, high fat type of diet; (2) the high carbohydrate, low fat type; (3) the high carbohydrate, low fat, low calorie type; and (4) the moderately high carbohydrate, moderately low fat type of diet.

Each of these systems of dieting has its supporters. For example, New-burgh and his associates (1) (2) (3) maintain that the carbohydrate content of the diabetic's food should be kept very low and that fat may be used to supply the necessary amount of energy. This method is purported, among other things, to allow for a sufficiently high caloric intake and at the same time to minimize the need for exogenous insulin. Petrén (4) and Rosen-berg (5) also subscribe to the same policy. The custom of prescribing low carbohydrate diets was the method of necessity if not of choice before the introduction of insulin, and it still enjoys some measure of popularity with physicians at the present time. In opposition to it, however, there has evolved the practice of prescribing diets of greater carbohydrate content in which the fat values are less than those which were employed formerly. The principal exponents of the high carbohydrate diets in diabetes have been Sansum *et alii* (6) (7) (8), Nixon (9), Aldersberg and Porges (10) (11), Geyelin (12), and Rabinowitch (13) (14). Such diets have been popularized by numerous writers subsequently and they are now so well known that further elaboration regarding their composition is unnecessary. Suffice it to say, that in contrast with the previous conceptions regarding the dietetic control of diabetes, the change to the high carbohydrate system seemed to be rather extreme in the allowed amounts of carbohydrate-bearing foods. Nevertheless, the published reports of the effects of these diets appeared to be favourable and, apart from other considerations, they were undoubtedly more adequate in all the nutritional requirements, as confirmed by Kysar and Northrup (15). Rabinowitch (14), while supporting the high carbo-hydrate type of diet, claims that the benefit depends upon a low caloric intake and a reduction of fat in the food to a minimum. Joslin (16) has chosen a middle course and, while acknowledging the possible merits of the aforementioned systems, relies upon a diet which is moderately rich in carbohydrate and moderately poor in fat. He stresses also the matter of moderation as regards the total calories and the protein. This so-called conservative method of treatment enjoys a wide popularity.

Many arguments based upon practical, experimental, and theoretical con-siderations have been advanced in support of the various dietary systems referred to above. The inference is that diabetes is a condition which responds to a variety of dietetic measures, but the statement does not supply an answer to the question which type of diet is most efficacious in the treatment of the patient.

An investigation was undertaken to compare the relative values from several points of view, of the various diets which have been advocated for use by diabetics. The primary object was to determine the optimum type of diet, if such there be, for the diabetic.

For this purpose, a series of twenty-seven trained diabetics of different ages with varying grades of severity of uncomplicated diabetes were subjected for various lengths of time to the effects of different test diets which were representative of those advocated for the control of the disease. Observa-

tions were recorded of the influence of these diets upon the patients' daily insulin requirements, the variations in the blood-sugar concentration, the glycosuria, ketonuria, changes in the blood cholesterol, and in the tolerance for glucose.   Also, as a practical aspect of the problem, the relative acceptability of the several diets from the patients' point of view, and the effect of the different diets on the sense of well-being of the individuals were noted. The patients who were selected for these tests comprised eighteen individuals who were studied under strict hospital surveillance and nine cases who attended regularly at the out-patient clinic for diabetics at the Victoria Hospital and whose reliability was dependable.

Experimental Procedures

1. *The test diets* employed in the investigation were arranged as follows: the energy values were computed on the basis of 25 calories per kg. of normal body weight for patients at rest in bed and 30 calories per kg. for ambulant patients, except as otherwise stated in the protocols.   The diabetic condition in every instance was stabilized first of all on a so-called standard test diet in which the protein supplied 15 per cent., the fat 60 per cent., and the carbohydrate 25 per cent. of the total calories.   This diet constituted a starting-point from which to proceed with the various changes in the quantities of fat and carbohydrate.   The protein allowance remained constant for each individual patient throughout the course of the observations.   The standard test diets served not only as a beginning for the conduct of the experiments, but also as examples of the so-called conservative type of diet such as that favoured by Joslin (16).

In the typical high fat, low carbohydrate type of diet, as recommended by Newburgh (1) (2) (3), the fat formed 75 per cent. and the carbohydrate 10 per cent. of the total calories; whereas in the high carbohydrate, low fat diet such as advocated by Rabinowitch (14), the fat comprised 22 per cent. and the carbohydrate 63 per cent. of the total calories.

While the modifications mentioned above constituted the principal avenues of approach to the problem, the effects of other dietary changes were also investigated.   For instance, in certain cases, fat was added to an existing high carbohydrate ration in order to determine its influence upon the carbohydrate tolerance.   Still other diets with various combinations of carbohydrate and fat, as indicated in the accompanying tables, were employed in order to observe the effect of these food components in different amounts upon the sugar tolerance, the insulin requirements and the general well-being of the patients.   The total glucose value or the glucose equivalent of the diets was regarded as comprising 100 per cent. of the carbohydrate plus 58 per cent. of the protein plus 10 per cent. of the fat.

With a view to studying further the result of an increased intake of energy as such, without at the same time adding to the available glucose or

fat of the diets, absolute ethyl alcohol was administered in medicinal doses several times daily to certain of the patients as indicated in the tables. Each dose of alcohol was rendered palatable by dilution with 15 grm. of lemon juice to which 5 grm. of sugar and some soda water were added. The carbohydrate values of these ingredients were accounted for in the diet calculations. One gram of alcohol was considered to possess an energy value of seven calories.

2. *Methods*: The effects of the test diets were checked by the following methods of observation:

(a) *Urine analyses*. The twenty-four-hour urine samples of patients within the hospital were tested daily for glucose, aceto-acetic acid, and acetone. Sugar concentration was estimated by Benedict's quantitative method and the amount excreted in twenty-four hours recorded. The out-patients visited the clinic one afternoon each week, when a specimen of urine was obtained. The results of urinary tests performed by these patients themselves at home were also included in the records.

(b) *Blood-sugar estimations*. In the case of in-patients, the concentration of sugar in the venous blood in the morning fasting state was estimated twice weekly by the improved Folin-Wu (17) technique; 'post cibos' blood-sugar tests were secured once a week. The blood samples for these p.c. blood-sugars were obtained $1\frac{1}{2}$ hours after breakfast from patients who were not receiving insulin and four hours after breakfast in the insulin-treated cases. The out-patients had blood samples withdrawn for blood-sugar estimations in the early afternoon of the day of their visit to the clinic.

(c) *Blood-cholesterol estimations* in the whole blood were carried out periodically on the fasting and afternoon blood samples referred to above by the method described by Myers and Wardell (18).

(d) *Glucose tolerance tests*. At the end of many of the dietary periods glucose-tolerance tests were performed in which the blood-sugar concentration was determined in the fasting state and at half-hourly intervals for two hours following the ingestion of 50 grm. of dextrose.

(e) *Patients' opinions*. A careful record was kept of the opinions and preferences expressed by the patients as regards the attractiveness or other features of the various diets and the relative degrees of physical and mental well-being occasioned by their use.

Results

The results of 112 different dietary combinations as applied in twenty-seven diabetics according to the methods outlined above are summarized in the accompanying tables and charts. Since the laboratory data regarding the hospital patients are not quite comparable with those of the out-patients, the findings are presented separately as two groups in Tables I and II respectively. The test diets are referred to by numbers and their actual

food values are shown.   For conciseness, the results of the sugar-tolerance tests are reduced to a figure which represents the percentage average increase of the blood sugar after the ingestion of the glucose as compared with the fasting value.   Thus changes in the tolerance of the individual patients are indicated.

A notable effect of the high fat, low carbohydrate diet, as previously recorded by Newburgh (2) (3) was a reduction of the amount of insulin which was required to be injected.   Only one patient needed insulin while receiving this type of diet.   He had severe diabetes (Table I, Case 5) and the reduction of the insulin dosage following a change from the conservative diet to a high fat, low carbohydrate diet of equal caloric value was slight and not commensurate with the reduction of the carbohydrate intake ; which fact showed a necessity for a relatively large amount of insulin as compared with the available glucose of the diet and suggested perhaps an antagonism between fat and insulin.

Even although the high fat, low carbohydrate type of diet diminishes the necessity for extrinsic insulin, a factor of undoubted practical importance, it possesses points which outweigh that virtue.   It may be criticized justifiably on the ground of its tendency to favour the development of ketonuria, a condition which, as emphasized by Himsworth (19), is to be avoided if possible.   The existence of a ketosis under these circumstances may be a factor in maintaining a demand for insulin, as mentioned by Graham, Clark, and Robertson (29).   The reduction of the carbohydrate allowance to a minimum does not necessarily result in an improvement of the diabetic's tolerance for carbohydrate.   Indeed, the contrary may obtain.   For instance, in Case No. 2 (Table I), the sugar tolerance test which was performed at the end of the high fat, low carbohydrate, period showed a decline in the patient's ability to deal with ingested dextrose as compared with the results of the test following the use of diets containing greater amounts of carbohydrate.   As a further example, Case No. 19 (Table II) progressed satisfactorily on a low carbohydrate, moderately high fat diet (Diet No. 6) without insulin for three months, when a gradual increase of the blood-sugar supervened and an amount of insulin equal to that required on a diet containing much more carbohydrate but less fat (Diet No. 5) was necessary. Such observations are in opposition to the statements of Newburgh and Waller (3) who maintain that a patient's carbohydrate tolerance is independent of the type of diet which he ingests.   Whether the apparent reduction of tolerance on the high fat, low carbohydrate type of diet was a result of the high fat or of the low carbohydrate values will be discussed later in this paper.

A practical aspect of the high fat, low carbohydrate dietary system, relates to the fact that every patient except one found it to be obnoxious mainly on account of its low satiety properties due to a paucity of the starchy foods.   Also, many patients registered a distaste for the so-called diabetic foods which entered into the composition of this type of diet.   The

only patient (Case No. 3) who did not object to a high fat ration had become inured to a low carbohydrate intake because she found that this caused her less gastro-intestinal discomfort than foods with greater bulk and more liberal carbohydrate values. On the whole, however, the patients experienced a less normal state of physical well-being and vigour on the high fat, low carbohydrate régime than on diets which contained less fat and more carbohydrate.

A rather remarkable feature, which has been commented upon by numerous writers and which was exemplified in this investigation, concerns the large amounts of carbohydrate foods which can be tolerated without apparent harm by many diabetics, especially those of more advanced years and those who exhibit the less severe forms of the disease. It is true, however, that a sudden change from a low to a high carbohydrate diet is followed frequently by a temporary rise of the blood-sugar and a transient increase of the output of dextrose in the urine. In many cases, however, a readjustment ensues and a satisfactory control of the situation is subsequently accomplished.

A difficulty which has been mentioned by certain observers (20) (8), and which was demonstrated in this investigation, concerns the regulation of the insulin dosages of patients on a high carbohydrate intake in view of the rapid fluctuations from hyperglycaemia to hypoglycaemia and the resulting tendency for the development of insulin reactions. Ellis (21) was able to counteract the instability of the blood-sugar by the administration of glucose and insulin in divided doses at frequent intervals. In the present investigation it was observed that when the fat content of the diet was increased, as in Case No. 5, the insulin reactions did not occur as readily as with a low fat intake, suggesting that fat may influence the output of endogenous insulin, or that it may modify in some way the activity of injected insulin. Thus, the fat of the diet, within certain limits, may exert a ' buffer' effect upon the blood-sugar reducing property of insulin, which is hardly explainable on the basis of an increase of the theoretical glucose value of the diet by reason of the glycerol of the added fat.

One-half the number of patients who were subjected to the sugar tolerance test at the end of a high carbohydrate, low fat dietary test period presented evidence of an improvement of the carbohydrate tolerance. Another observation suggestive of a more perfect utilization of carbohydrate on the high carbohydrate régime was that the amount of glucose metabolized per unit of exogenous insulin was obviously greater than with the low carbohydrate diets.

All the patients, except Case No. 3, preferred the higher to the lower carbohydrate diets, but they objected to a very small allowance of fat. The preference for the higher carbohydrate ration seemed to depend upon the greater satiety value of the carbohydrate foods; also, because a sufficient variety of appetizing foods was allowable, a more natural sense of physical and mental well-being was attained.

The fact that the continued use of a high carbohydrate diet does not necessarily cause a decline of the tolerance for carbohydrate is exemplified in Case No. 22 (Table II) who, after nine months of high carbohydrate intake, did not require an increased dosage of insulin.   This is in contrast to Case No. 19 (Table II) referred to above, who required an addition of insulin on the continuance of a low carbohydrate diet.   It was noted especially among the out-patient group of subjects that the individuals who had subsisted upon diets markedly restricted in carbohydrate for some time before the test diets, had lost their desire for sweet foods and, therefore, objected to them.   Rather, they preferred an amount of carbohydrate which would be contained in foodstuffs such as bread, vegetables, and fruits.

The effect of adding fat in moderate amounts (up to a total intake of from 70 to 125 grm. of fat a day, with a corresponding increase of the total calories) to the pre-existent low fat diets were observed in seventeen cases. No conclusive evidence of improvement or the reverse in the carbohydrate tolerance was noted as a result of such increases.   There was, however, definite indication that these diets were much more popular with the patients than those which contained a minimal amount of fat.   All the subjects except one favoured the addition of the fat.   As well as possessing a liberal amount of carbohydrate, these diets supplied sufficient fat to make the meals palatable.

The effects of still greater amounts of fat (up to a total of from 125 to 200 grm. of fat per day) were studied in nineteen cases, and the general trend of events toward an impairment of the carbohydrate tolerance. A variety of opinions were expressed regarding the acceptability of these diets.   Several patients preferred them while others disliked them on account of their high fat content and relatively large bulk.

Two mildly diabetic individuals (Cases Nos. 2 and 9) were given 250 grm. of fat a day in addition to a high carbohydrate allowance.   In both instances the caloric values of the diets were much in excess of the optimum for the individuals.   One of these patients became nauseated by the ingestion of such large quantities of fat, and an impairment of sugar tolerance was demonstrated in both.

It would appear, therefore, that the addition of fat to a high carbohydrate diet does not produce any serious impairment of carbohydrate tolerance unless the fat exceeds 125 grm. a day.   In excess of this quantity, the fat seems to affect the tolerance for carbohydrate in a deleterious manner, and as a result an increased demand for insulin is created. Czoniczer and Kolta (22) conclude that the optimum amount of fat in a high carbohydrate diet is approximately 100 grm. per day, an observation which is substantiated by the present results.

It has been claimed (7) (23) that the number of grams of fat and carbohydrate in the diet of a diabetic could be transposed without impairing the carbohydrate tolerance of the individual.

It will be observed that in Case No. 4 (Table I), 96 grm. of fat were

replaced by 100 grm. of carbohydrate with a consequent addition of 90 grm.
to the total glucose value of the diet and a reduction of 460 calories per
day. As a result of this change, there was an increase of only four units
in the daily amount of insulin which was given. The indications were,
therefore, that the apparent improvement in the tolerance for carbohydrate
depended upon either the raised glucose equivalent of the diet due to the
increased carbohydrate intake; or on the reduction of the fat, or the
reduction of the total number of calories; or on a combination of these
factors. An attempt was made to determine which of these possibilities
was the influential one.

First, the effect of added calories was studied. For this purpose addi-
tional calories without additional carbohydrate or fat were provided by
supplementing the food intake with alcohol after the manner of the previous
investigations of Allen and Wishart (24), Leclercq (25), and Fuller (26).
Of the six cases tested, the insulin requirement was unaltered in three cases
and it was actually reduced in one. The other two patients were not
receiving insulin and they did not exhibit any appreciable change of their
blood-sugar concentrations. In every instance, there was an obvious im-
provement in the carbohydrate tolerance according to the results of the
glucose tolerance tests as compared with the findings obtained with the
same diets without the alcohol. Alcohol in medicinal doses may have a
beneficial effect, therefore, upon the carbohydrate metabolism of diabetics,
a deduction which is not without foundation on the grounds of clinical
experience (27) (28). The present observations indicate also that an increase
of approximately 500 calories a day does not exert a detrimental effect
upon the diabetic's tolerance for carbohydrate. This observation lends
support to the remarks of Graham, Clark, and Robertson (29) whose ex-
perience led them to conclude that the benefit to be derived from a higher
carbohydrate type of diet in diabetes was not due to a decrease in the
caloric value of the diet. The diabetic's carbohydrate tolerance must be
related, therefore, more to the total available glucose and the fat content
of the diet than to the daily caloric intake. It is noteworthy in this regard
also, that Eason and Lyon (30) concluded that the insulin requirement of a
diabetic appeared to be more closely related to the total grams of food-stuff
$(C + P + F)$ consumed than to the total calories.

When the daily allowance of alcohol was replaced by an equicaloric
amount of fat which caused the glucose content of the diets to be increased
by approximately five grams only, the carbohydrate tolerance was found to
be diminished, as shown by an increase of the insulin requirements and by
more abnormal glucose tolerance curves. An increment of 55 grm. of fat
had a more deleterious influence upon the tolerance for carbohydrate than
an equivalent number of calories supplied in the form of alcohol.

The blood cholesterol is considered by many to serve as an index of the
degree of severity and of the progress of diabetes. From estimations on
forty healthy individuals, Hunt (31) took the normal range of the cholesterol

to be from 118 to 272 mg. per cent. Rabinowitch (14) regards the upper limit of normality to be 180 mg. per cent. A normal cholesterol, according to his reasoning, indicates that the fundamental disturbance of metabolism is under control and his high carbohydrate, low fat, low calorie diet is intended to avoid hypercholesterolaemia. A similar view has been expressed by Dyke (32). In the present investigation, Rabinowitch's figure of 180 mg. per cent. was accepted as the upper bound of the normal for the whole blood cholesterol, and no consistent changes in the cholesterol values occurred as a result of the different types of diets. High levels were found frequently at the beginning of the investigation which fell to low levels subsequently irrespective of the treatment instituted, but when the fat content of the diets was increased greatly there was some tendency towards an increase of the blood cholesterol. An explanation as to why the initial values were not higher in the cases referred to in this paper may rest in the fact that most of the patients had already been under treatment, many for long periods of time; for that reason their metabolic abnormalities were partially, if not completely, under control beforehand.

Discussion

A clinical investigation of this kind cannot be pursued with anything approaching the degree of accuracy which prevails in the case of experiments conducted within a research laboratory. Both the disease and the human material are too variable. Since few diabetics are completely diabetic, the majority tend to improve, especially under conditions of hospital supervision, regardless of the mode of treatment, provided that the latter is not grossly irrational, and that conditions which are not readily controllable, such as mild infections, do not cause adverse fluctuations of the carbohydrate tolerance. Factors, such as the above, render difficult any attempt to compare truthfully the relative merits of different therapeutic measures, particularly those involving the use of special diets. The tendency for a progressive improvement of the carbohydrate tolerance throughout the course of certain of the observations herein reported is obvious. There was a great variation in the response of different patients to identical diets. Also, it was noted that certain individuals would respond differently to the same diet at different times.

Observations such as these emphasize that the dietetic treatment of diabetes may be standardized in respect to certain broad principles, but cannot be standardized as to details. The control of this disease must remain an individual problem to be worked out in accordance with the conditions which prevail in the particular case.

Concerning principles, however, the practice of allowing more liberal carbohydrate diets than was the custom a decade ago deserves commendation. There has accumulated considerable evidence in support of the

modern views, ranging from the observations of Hamman and Hirsch-
mann (33) who demonstrated in both normal and diabetic individuals that
the ingestion of a second dose of glucose caused a less pronounced rise of
the blood-sugar than a similar amount of glucose taken a short time before,
to the recent investigations of Himsworth (34, 35, 36) who showed that
carbohydrate starvation caused the sugar tolerance to be lowered and
that the administration of carbohydrate caused it to be increased.   Clinical
experiences have verified to a considerable degree the results of the laboratory
investigations.   It has been proved that major increases of the carbo-
hydrate can be made in the diets of many diabetics with little or no increase
of the insulin requirement or of the blood-sugar.   In some cases the demand
for insulin is actually decreased.

The expression, high carbohydrate, as applied in this respect should be
a relative rather than an absolute term and not refer to any particular
allowance of this type of food.   It is true that some diabetics thrive on
what would have been considered formerly impossibly rich carbohydrate
diets, while others can be controlled with difficulty on diets providing
carbohydrate values little, if any, above those which prevailed in the pre-
insulin years.   Consequently, the use of the term *higher* carbohydrate diets,
as adopted by some writers, is preferable.

With regard to the influence of fat upon the carbohydrate tolerance of
the diabetic, the evidence is less conclusive than in the case of the carbo-
hydrate foods.   The observations herein reported tend to confirm the belief
of Rabinowitch (14) and the experimental results of Himsworth (34, 35)
that an excess of fat decreases the sugar tolerance.   Whether or not the
fat intake should be reduced to a minimum is a debatable point.   One
virtue in keeping the fat in the diet low concerns the limitation of the
caloric intake and consequently the control of the body weight.

Under-nutrition as a factor conducive to the successful treatment of
diabetes is a feature which has been carried forward from the pre-insulin
era into the insulin era.   Allen (24, 37) emphasized the importance of
respecting the limitation of total assimilation in diabetes and the principle
which he reiterated still prevails with certain modifications.   In confirmation
of the view that the harmfulness of excessive fat in diabetes does not consist
merely in its possible conversion into sugar or acetone, but rests pre-eminently
in the overload of the total metabolism, Allen (24) and Leclercq (25) showed
that the administration of alcohol in quantities which exceeded the caloric
tolerance of the individuals produced a return of glycosuria and other
manifestations of diabetes.   On the other hand, Fuller (26) observed that
the immediate effect of alcohol was to reduce both hyperglycaemia and
glycosuria in most cases of mild or moderate diabetes, an effect which was
most pronounced when the alcohol was substituted for the caloric equivalent
of fat, but which also was frequently manifested when the alcohol was given
as an addition to the previous diet.   These effects, however, were frequently
lacking in diabetic cases of great severity.   Likewise, Hunt (28) postulated

a salutary effect of alcohol upon the carbohydrate metabolism, although the ingestion of rapidly absorbed alcohol along with glucose resulted in a higher concentration of blood-sugar than was occasioned by a similar amount of glucose without alcohol. The results obtained with the use of alcohol in the present investigation tend to concur with those of Fuller (26) and Hunt (28). While the problem of the influence of added calories *per se* remains unsolved, the evidence as presented tends to attribute the undesirable effect of excessive fat rations upon the carbohydrate tolerance to some phenomenon peculiar to the metabolism of fat rather than to the increased total metabolism as represented by the total calories. The practical aspect of the matter seems to be that certain diabetics may be allowed a relatively liberal carbohydrate and caloric diet provided that the fat intake is kept reasonably low, i.e. 125 grm. or less a day, but the factors of major importance in determining an individual's requirement for insulin are the degree of severity of the diabetic tendency and the total glucose value of the diet.

Summary

1. Twenty-seven trained diabetics of various grades of severity have been studied on several different diets, using the necessary amount of insulin.

2. The high fat, low carbohydrate type of diet caused the daily amount of insulin required by many of the patients while on other diets to be greatly reduced or eliminated entirely. The requirement for insulin, however, was greater in proportion to the total glucose content of the diet than with the higher carbohydrate, lower fat types of diets. The low carbohydrate, high fat diet tends to cause a decline in the carbohydrate tolerance, also to favour ketonuria.

3. Many of the patients could tolerate a high carbohydrate diet providing the fat was kept low. Raising the carbohydrate intake did not require increase of the insulin dosage because a higher carbohydrate diet caused an improvement of the tolerance.

4. The most satisfactory tolerance for carbohydrate was observed when the fat content of the diet was approximately 100 grm. per day. When the daily fat intake exceeded 125 grm., a diminution of carbohydrate tolerance ensued.

5. Diets which contained a minimum amount of fat were not appreciated as much as the diets which contained a slightly larger amount. The most acceptable diet from the patient's point of view was one which supplied a liberal carbohydrate allowance with a fat ration of approximately 100 grm. a day. This type of diet earned its popularity by approaching most nearly a normal dietary; by being less expensive and more readily obtainable and easier prepared than a diet in which the carbohydrate was restricted rigidly. The so-called conservative type of diet which provided a moderately high allowance of carbohydrate and a moderately low allowance of fat most nearly supplied these conditions.

6. The insulin requirement seemed to depend more upon the total available glucose content of the diet than upon its total caloric value.

7. The higher carbohydrate diets for diabetics promote a state of physical well-being and therefore are more conducive to co-operation on the part of the patients.

8. The type of diet which is best adapted for a particular patient must be governed by individual requirements.

9. There was no conclusive evidence that the blood cholesterol concentration varied appreciably with the fat content of the diet.

REFERENCES

1. Newburgh, L. H., and Marsh, P. L., *Arch. Int. Med.*, Chicago, 1923, xxxi. 455.
2. Newburgh, L. H., *Ann. Int. Med.*, Ann Arbor, ii. 645.
3. Newburgh, L. H., and Waller, D. S., *Journ. Clin. Invest.*, N. York, 1932, xi. 995.
4. Petrén, K., *Münch. med. Wchnschr.*, 1927, lxxiv. 1123.
5. Rosenberg, M., *Deutsche med. Wchnschr.*, Leipz., 1933, lix. 320.
6. Sansum, W. D., Blatherwick, N. R., and Bowden, R., *Journ. Amer. Med. Assoc.*, Chicago, 1926, lxxxvi. 178.
7. Sansum, W. D., Gray, P. A., and Bowden, R., *The Treatment of Diabetes Mellitus with Higher Carbohydrate Diets*, N. York, 1929.
8. Gray, P. A., and Sansum, W. D., *Journ. Amer. Med. Assoc.*, Chicago, 1933, c. 1580.
9. Nixon, J. A., *Brit. Med. Journ.*, Lond., 1930, i. 326.
10. Aldersberg, D., and Porges, O., *Klin. Wchnschr.*, Berl., 1926, v. ii. 1451 and 1508. Aldersberg, D., and Porges, O., *ibid.*, 1927, vi. ii. 2371.
11. Aldersberg, D., and Porges, O., *Presse méd.*, Paris, 1933, xli. 400.
12. Geyelin, H. R., *Atlantic Med. Journ.*, Harrisburg, 1926, xxix. 825.
13. Rabinowitch, I. M., *Canad. Med. Assoc. Journ.*, Montreal, 1930, xxiii. 489.
14. Rabinowitch, I. M., *Diabetes Mellitus*, Toronto, 1933.
15. Kysar, R. G., and Northrup, M. W., *Journ. Amer. Dietetic Assoc.*, Chicago, 1930, vi. 118.
16. Joslin, E. P., *The Treatment of Diabetes*, Philad., 1928, 565.
17. Folin, O., *Journ. Biol. Chem.*, Balt., 1930, lxxxvi. 173.
18. Myers, V. C., and Wardell, E. L., *ibid.*, 1918, xxxvi. 147.
19. Himsworth, H. P., *Lancet*, Lond., 1934, ii. 888.
20. Poulton, E. P., *ibid.*, 1931, i. 351.
21. Ellis, A., *Quart. Journ. Med.*, Oxford. 1934, N.S. iii. 137.
22. Czoniczer, G., and Kolta, E., *Med. Klin.*, Berl., 1932, xxviii. 752.
23. Richardson, R., *Amer. Journ. Med. Sci.*, Philad., 1929, clxxvii. 426.
24. Allen, F. M., and Wishart, M. B., *Journ. Metabol. Res.*, Morristown, 1922, i. 281.
25. Leclercq, F. S., *ibid.*, 1922, i. 307.
26. Fuller, L. S., *ibid.*, 1922, i. 609.
27. Williamson, R. T., *Diabetes Mellitus and its Treatment*, Edinb., 1898, 363.
28. Hunt, T. C., *Lancet*, Lond., 1930, i. 121.
29. Graham, G., Clark, A., and Robertson, H. E. W., *ibid.*, 1932, ii. 990.
30. Eason, J., and Lyon, D. M., *ibid.*, 1933, i. 743.
31. Hunt, H. M., *New Eng. Journ. Med.*, Boston, 1929, cci. 659.
32. Dyke, S. C., *Lancet*, Lond., 1932, i. 978.
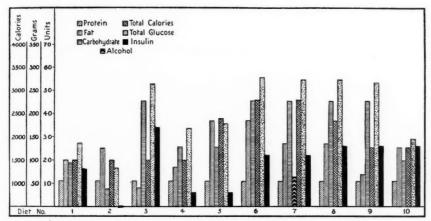
33. Hamman, L., and Hirschman, I. I., *Bull. Johns Hopkins Hosp.*, Balt., 1919, xxx. 306.

34. Himsworth, H. P., *Clin. Sci.*, Lond., 1933, l. 1.
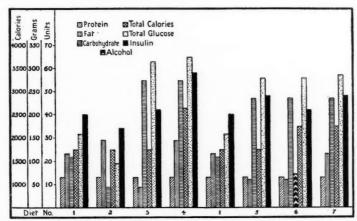
35. Himsworth, H. P., *Journ. Physiol.*, Camb., 1934, lxxxi. 29.

36. Himsworth, H. P., *Brit. Med. Journ.*, Lond., 1934, ii. 57.

37. Allen, P. M., Stillman, E., and Fitz., R., *Total Dietary Regulation in the Treatment of Diabetes*, N. York, 1919.

Case 1. Showing the relationship of the dietary constituents and the daily insulin requirement.

Case 5. Showing the relationship of the dietary constituents and the daily insulin requirement.

TABLE I

Patients Observed in the Hospital

Case no.	Age (years)	Sex	Diet no.	Days on diet	Diet Prot. (grm.)	Fat (grm.)	Carbo. (grm.)	Alcohol (grm.)	Calories	Total glucose value (grm.)	Insulin (units) per day	Blood-sugar (mg. %) a.c./p.c.	Bl. cholesterol (mg. %)	Glycosuria	Ketonuria	Glucose tol. test % increase of blood-sugar	Remarks
1	57	F	1	16	56	100	94	—	1,500	136	16	121/—	250	0	0	—	Moderately severe diabetes. Preferred diet No. 9. Liked starchy foods, not sugars. Did not feel as well on high F, low C.
			2	16	56	125	38	—	1,500	83	0	78/—	250	0	T	—	
			3	24	56	40	228	—	1,500	264	34	106/—	266	T	0	—	
			4	45	56	85	128	—	1,500	169	6	99/141	170	0	0	—	
			5	10	56	185	128	—	2,400	179	6	96/133	150	0	0	—	
			6	20	56	185	228	64	2,800	279	22	91/132	200	0	0	243	
			7	17	56	135	228	—	2,800	274	22	138/132	130	0	0	186	
			8	31	56	135	228	—	2,350	274	26	136/166	100	T	0	249	
			9	23	56	70	228	—	1,765	267	26	102/103	110	T	0	236	
			10	11	56	127	100	—	1,765	145	26	104/98	100	0	0	—	
2	71	F	1	16	62	110	103	—	1,650	150	0	87/—	210	0	0	—	Mild diabetes. Preferred high C. diets. Nauseated by high F. diets.
			2	17	62	137	41	—	1,650	91	0	76/—	150	0	0	—	
			3	16	62	40	260	—	1,650	300	0	83/—	160	0	0	—	
			4	16	62	110	260	—	2,280	307	0	87/—	130	0	0	—	
			5	16	62	160	260	—	2,730	312	0	96/140	140	0	0	216	
			6	18	62	200	260	—	3,090	316	0	111/161	160	0	0	203	
			7	27	62	250	260	—	3,540	321	0	122/135	125	0	0	192	
			3	23	62	40	260	—	1,650	300	0	93/198	114	0	0	211	
			1	30	62	110	103	—	1,650	150	0	137/143	100	0	0	255	
			2	39	62	137	42	—	1,650	92	0	88/117	140	0	0	—	

No.	Age	Sex							Cals.								Remarks
3	64	F	1	16	59	105	98	—	1,575	143	18	92/—	111	0	0	—	Moderately severe diabetes. Preferred low C., due to its low residue. High C. caused flatulence and diarrhoea.
			2	17	59	131	40	—	1,575	87	0	92/—	143	0	0	—	
			3	16	59	39	248	—	1,575	286	22	99/—	173	0	0	—	
			4	16	59	80	248	—	1,945	290	18	67/114	133	0	0	—	
			5	15	59	100	248	—	2,125	292	28	125/164	110	0	0	—	
			6	5	59	150	248	—	2,575	297	28	110/131	100	0	0	—	
4	8	F	1	17	66	116	110	—	1,750	160	14	118/—	166	0	0	—	Severe diabetes. Preferred diet No. 4. Not controlled on high C. low F. Total cals. = 50 cals. per kg. of normal wt.
			2	15	66	146	44	—	1,750	97	0	93/—	160	T	T	—	
			3	7	66	43	275	—	1,750	318	32	212/—	—	+	+	—	
			2	5	66	146	44	—	1,750	97	0	—	—	+	+	—	
			4	20	66	101	144	—	1,750	192	22	145/105	130	+	0	—	
			2	4	66	146	44	—	1,750	97	0	94/—	—	+	0	—	
			5	8	66	50	144	—	1,290	187	26	87/—	190	T	0	—	
5	27	M	1	31	65	116	109	—	1,740	158	40	149/—	145	T	0	—	Severe diabetes. More insulin reactions on high C., low F. diets.
			2	17	65	145	44	—	1,740	96	34	180/—	143	T	0	—	
			3	21	65	43	273	—	1,740	315	42	229/—	100	+	0	—	
			4	10	65	143	273	—	2,640	325	58	115/124	80	T	0	148	
			1	17	65	116	109	—	1,740	158	32	204/161	70	+	0	136	
			5	25	65	60	235	—	1,740	279	48	417/176	85	+	0	136	
			6	22	65	60	235	72	2,244	279	42	263/132	112	+	0	—	
			7	16	65	116	235	—	2,244	285	48	175/115	110	T	0	—	
6	43	F	1	16	60	106	99	—	1,590	144	0	90/—	260	0	0	—	Moderately severe diabetes. Disliked C.-rich foods, e.g. bread, potatoes, sugar, and marmalade.
			2	16	60	132	40	—	1,590	88	0	90/—	296	0	0	—	
			3	20	60	40	248	—	1,590	286	18	90/78	200	0	0	—	
			4	13	60	140	248	—	2,490	297	10	101/90	133	0	0	—	
			5	11	60	200	248	—	3,030	303	10	94/—	80	0	0	151	
7	50	M	1	16	76	136	128	—	2,040	186	0	87/—	170	0	0	—	Mild diabetes. Felt better on high C. high cal. diets.
			2	9	76	170	51	—	2,040	112	0	73/—	150	0	0	—	
			3	10	76	50	321	—	2,040	370	0	106/—	125	0	0	—	
			4	17	76	150	321	—	2,940	380	0	90/210	120	+	0	—	
			5	11	76	200	321	—	3,390	385	0	104/217	100	+	0	—	
8	49	M	1	16	64	113	107	—	1,700	155	14	124/—	222	0	0	—	Moderately severe diabetes. Preferred high C., high cal. diet.
			2	17	64	42	267	—	1,700	308	18	112/162	140	0	0	—	
			3	11	64	142	267	—	2,600	318	18	109/—	150	0	0	—	

TABLE I (continued)

Case no.	Age (years)	Sex	Diet no.	Days on diet	Prot. (grm.)	Fat (grm.)	Carbo. (grm.)	Alcohol (grm.)	Calories	Total glucose value (grm.)	Insulin (units per day)	Blood-sugar (mg. %) a.c./p.c.	Bl. cholesterol (mg. %)	Glycosuria	Ketonuria	Glucose tol. test % increase of blood-sugar	Remarks
9	50	F	1	14	66	117	109	—	1,750	159	0	94/—	180	0	0	—	Mild diabetes. Preferred high C. diets. High cal. diets not suitable.
			2	9	66	43	275	—	1,750	318	0	60/95	130	0	0	—	
			3	17	66	143	275	—	2,650	328	0	75/65	130	0	0	—	
			4	21	66	200	275	—	3,165	333	0	87/80	121	0	0	192	
			5	33	66	250	275	—	3,615	338	0	79/80	121	0	0	192	
			6	28	66	195	275	72	3,120	333	0	97/—	120	0	0	151	
10	50	M	1	12	64	113	107	—	1,700	155	0	77/—	122	0	0	—	Mild diabetes. Preferred high C., high cal. diet.
			2	9	64	42	267	—	1,700	308	0	69/81	133	0	0	—	
			3	9	64	192	267	—	3,050	323	0	70/94	125	0	0	—	
11	79	M	1	7	64	115	108	—	1,725	156	0	66/—	135	0	0	—	Mild diabetes. Preferred high C. diet.
			2	7	64	45	265	—	1,725	307	0	79/—	135	0	0	—	
			3	7	64	145	265	—	2,625	317	0	88/171	—	0	0	—	
12	48	F	1	8	57	102	95	—	1,525	138	0	80/—	180	0	0	—	Mild diabetes. Preferred high C., high cal. diets.
			2	9	57	38	238	—	1,525	275	0	82/114	166	0	0	—	
			3	17	57	138	238	—	2,425	285	0	98/126	100	0	0	—	
			4	8	57	200	238	—	2,980	291	0	93/—	105	0	0	—	
13	46	F	1	9	62	110	103	—	1,650	150	0	121/—	190	0	0	—	Mild diabetes. Preferred high C. diet.
			2	9	62	40	260	—	1,650	300	0	130/—	160	T	0	—	
14	78	F	1	12	61	108	102	—	1,625	148	0	74/79	120	0	0	—	Mild diabetes. Preferred high C. diet, disliked sugar.
			2	14	61	108	202	—	2,024	248	0	82/140	105	0	0	—	
			3	9	61	150	202	—	2,400	252	0	85/145	100	0	0	—	
15	60	F	1	37	64	113	107	—	1,700	155	18	123/107	133	0	0	212	Moderately severe diabetes. Disliked high C. due to greater residue. Refused to use marmalade.
			2	33	64	65	214	—	1,700	258	22	117/154	110	0	0	203	
			3	25	64	120	214	—	2,195	263	18	122/178	100	0	0	202	
			4	20	64	64	214	72	2,194	258	18	168/176	90	0	0	181	
			5	26	64	64	214	—	1,690	258	18	122/143	140	0	0	179	

(continuation of the preceding table — Cases 16–18)

Case no.	Age (years)	Sex	Diet no.	Weeks on diet	Prot. (grm.)	Fat (grm.)	Carbo. (grm.)	Calories	Total glucose value grm.	(—)	Insulin (units per day)	Blood-sugar (mg. %)	Bl. cholesterol (mg. %)	Glycosuria	Ketonuria	Remarks
16	82	M	1	9	67	118	111	1,775	162	—	0	160	208	71/105	0	Mild diabetes. Preferred high C. due to its greater satiety value.
			2	24	67	69	222	1,775	268	—	0	133	195	88/131	0	
			3	22	67	124	222	2,270	273	—	0	125	183	94/93	0	
			4	18	67	68	222	2,272	268	72	0	115	168	100/89	0	
17	43	F	1	9	56	100	94	1,500	136	—	18	100	249	89/73	0	Moderately severe diabetes. Preferred high C. due to its greater amount of starches.
			2	21	56	55	195	1,500	233	72	20	100	196	112/101	0	
			3	21	56	55	195	2,004	233	—	20	70	186	140/117	0	
			4	23	56	111	195	2,004	239	—	20	80	187	126/83	0	
			5	19	56	153	100	2,004	148	—	8	90	198	129/86	0	
18	45	F	1	11	59	105	99	1,575	144	—	0	90	288	74/137	0	Mild diabetes. Preferred diet No. 2.
			2	15	59	60	200	1,575	240	—	0	90	258	96/198	0	

TABLE II

Out-patient Group of Cases

Case no.	Age (years)	Sex	Diet no.	Weeks on diet	Prot. (grm.)	Fat (grm.)	Carbo. (grm.)	Calories	Total glucose value grm.	Insulin (units per day)	Blood-sugar (mg. %)	Bl. cholesterol (mg. %)	Glycosuria	Ketonuria	Remarks
19	53	F	1	6	65	116	109	1,740	158	6	107	195	0	0	Moderately severe diabetes; refused diet No. 2, too high C. Disliked sugar, marmalade, &c. Preferred diets 1 and 5.
			2	1	65	43	276	1,740	318	6	172	—	0	0	
			3	6	65	59	239	1,740	283	6	125	100	0	0	
			4	9	65	159	239	2,640	292	14	192	142	0	0	
			5	6	65	90	239	2,025	286	10	120	110	0	0	
			6	30	65	142	50	1,740	102	10	121	150	0	0	
20	59	F	1	5	68	120	112	1,800	163	6	159	180	0	0	Moderately severe diabetes; preferred diets No. 1 and 4.
			2	5	68	44	283	1,800	327	6	161	100	0	0	
			3	15	68	120	283	2,485	334	32	185	100	0	0	
			4	30	68	75	283	2,080	330	36	149	160	0	0	

TABLE II (continued)

Case no.	Age (years).	Sex.	Diet no.	Weeks on diet.	Prot. (grm.)	Fat (grm.)	Carbo. (grm.)	Calories.	Total glucose value grm.	Insulin (units per day).	Blood-sugar (mg. %).	Bl. cholesterol (mg. %).	Glycosuria.	Ketonuria.	Remarks.
21	56	F	1	5	73	130	122	1,950	177	18	137	190	0	0	Moderately severe diabetes; disliked high C. Preferred diets No. 1 and 4. High C, low F—tolerance increased.
			2	5	73	48	307	1,950	354	14	122	100	0	0	
			3	6	73	130	307	2,690	362	18	153	90	0	0	
			4	9	73	100	189	1,950	241	14	153	120	0	0	
			5	15	73	75	245	1,950	295	8	122	130	0	0	
22	57	F	1	5	73	130	122	1,950	177	16	123	170	0	0	Moderately severe diabetes. Liked moderately high C.
			2	8	73	48	307	1,950	354	28	222	100	0	0	
			3	11	73	75	245	1,950	295	28	133	100	0	0	
			4	28	73	110	245	2,260	298	22	127	140	0	0	
23	54	M	1	5	91	162	152	2,430	221	44	132	133	+	0	Severe diabetes. Liked bread and potatoes, not jam and sugars. Preferred high C.
			2	7	91	118	252	2,430	317	50	82	114	++	0	
			3	8	91	60	252	1,910	311	52	143	114	++	0	
			4	6	91	100	161	1,910	224	50	204	100	++	0	
			5	28	91	83	200	1,910	261	48	83	—	0	0	
24	18	F	1	6	45	80	75	1,200	109	48	143	270	0	+	Severe diabetes. High C., low F.—reduced tolerance. Order of preference of diets, 3, 2, 4, 1.
			2	11	45	50	143	1,200	174	60	267	150	++++	++	
			3	7	45	69	100	1,200	133	66	162	100	++	++	
			4	31	45	78	80	1,200	114	52	117	181	0	0	
25	69	F	1	5	75	134	126	2,010	183	54	176	170	0	0	Severe diabetes. Refused diet 2, too high C.
			2	2	75	50	315	2,010	364	54	194	130	++	0	
			3	16	75	50	237	1,700	333	48	116	100	0	0	
26	53	M	1	3	93	166	155	2,490	226	36	121	100	0	0	Severe diabetes. Preferred diet No. 2.
			2	4	93	61	392	2,490	452	44	178	121	+	0	
27	48	F	1	8	74	132	124	1,980	180	60	137	200	++	0	Severe diabetes. Preferred diet No. 2. Tolerance improved on No. 2 and patient felt better on it.
			2	7	74	60	286	1,980	335	60	194	135	++	0	
			3	5	74	74	200	1,980	253	64	144	—	T	0	

THE TREATMENT OF TETANUS [1]

By LESLIE COLE

WITH OBSERVATIONS ON THE FATE OF INJECTED ANTITOXIN

By E. T. C. SPOONER

THIS review of twenty-one cases of tetanus is written with the aim of systematizing the treatment. All the cases described have been treated at Addenbrooke's Hospital, Cambridge, during the last seven years and have been personally observed by the author at least daily during the acute phases of the illness.

As the paper is concerned with treatment, no attempt will be made to describe the rarer manifestations of the disease. It is important however to bear in mind the various degrees of severity which occur, and the following artificial classification into four degrees is convenient:

1. That in which there is local tetanus only. (For examples, see Dean 19.)

2. That in which there is generalized tonic rigidity involving particularly the masseters, the muscles of the spine, chest, and abdomen and to a lesser extent the limbs. This rigidity gradually increases and then slowly passes off, the whole process lasting from one to four weeks. Reflex spasms and reflex excitability are slight or absent. (Case 1.)

3. That in which the tonic rigidity described in degree 2 passes into the stage of reflex spasms, occurring at intervals and brought on by the slightest stimulation. Such spasms persist for a few days to a fortnight and then cease, leaving the patient again in the state of tonic rigidity which slowly passes off. (Cases 2–11 and 16.)

4. That in which the spasms described in degree 3 come on rapidly, becoming progressively more frequent and prolonged until they are almost continuous, and death, often preceded by hyperpyrexia of 108–110°, takes place from cardiac or respiratory failure. (Cases 12–15, 17, and 18.)

Patients of the first and second degree have usually had antitoxin, or their wound is very slight. The incubation period is long, and they usually recover. Patients of the third degree may recover. Their incubation period is from about five to fourteen days. More of the fourth degree do not appear to recover under present treatment. They usually have an incubation period of four days or less.

[1] Received February 8, 1935.

Meyer and Ransom (1) and Permin (2) have shown how toxin absorbed from the wound spreads to produce symptoms, and that the severity of a case depends on the amount of toxin absorbed.

Treatment. When the symptoms of tetanus have appeared treatment must be directed along three lines: (1) Prevention of further absorption of toxin by the nervous system. (2) Prevention of exhaustion by control of spasms. (3) The giving of sufficient food. The earlier treatment is begun after the first symptom has appeared the greater is the chance of success. In most cases the precious hours are wasted before the diagnosis is made and antitoxin given. If the simple fact were remembered that stiffness of the jaw, especially if accompanied by pain in the back or abdomen, probably means tetanus or 'lockjaw', more lives might be saved.

Toxin is formed locally in the wound and reaches the motor cells of the central nervous system in the manner described. It is evident, however, that the first symptoms of tetanus appear when a certain amount of toxin has reached the nervous system, and that in most cases toxin is still at this stage passing into the nervous system from the wound and general circulation. In most cases symptoms will appear before a lethal dose has reached the nervous system, and the amount already there can in time be neutralized completely as shown by cases which recover. If, therefore, further inflow of toxin from the wound can be prevented soon enough, recovery is simply a matter of time.

Further absorption of toxin can be prevented, first, by removing the tetanus bacilli from the wound or rendering them inactive, and, secondly, by neutralizing toxin with antitoxin.

Antitoxin should be given before the wound is touched, because any manipulation or interference with the wound may cause more toxin to pass into the circulation, and if this occurs it is important that there shall be plenty of antitoxin already there to meet it.

The aim of antitoxin treatment is to bring antitoxin in contact with toxin in large amounts as soon as possible after the first symptoms have appeared. At this stage some toxin is still circulating in the blood where it clearly can most speedily be neutralized by a large intravenous dose of antitoxin.

By the time the first symptoms have appeared, however, some toxin is passing up the axis cylinders of the motor nerves, some has reached and become 'fixed' to the motor nerve cells, and some is diffusing into the nervous system. It is with the hope of neutralizing this toxin that the intrathecal and cisternal routes have been advocated. Whether this object can be attained better by intrathecal than by intravenous injection is still disputed. Ransom (3) states that toxin which has reached the nervous system is inaccessible to antitoxin. The problem can be studied from three angles; from a consideration of some points in the anatomy and physiology of the central nervous system, from certain animal experiments, and from clinical results.

Weed (4) has shown that the cerebrospinal fluid comes mainly from the choroid plexus, a small amount also passing out along the perivascular spaces to the subarachnoid space. From there it passes through the arachnoid villi into the venous sinuses. Fluid introduced into the theca will, therefore, tend to pass into the veins by the arachnoid villi and will not come at once into close contact with the nervous tissue. Weed has also shown that the normal direction of flow of the cerebrospinal fluid along the perivascular spaces can be reversed by the intravenous injection of hypertonic saline solution so that it passes by the perivascular spaces into the perineural spaces.

This suggests that the intrathecal route is inferior to the intravenous. All parts of the brain and spinal cord are richly supplied with blood-vessels and capillaries in close contact with the nerve-cells themselves. Antitoxin, therefore, would reach these nerve-cells more quickly when given directly into a vein than if it were first injected into the spinal theca and then absorbed into the venous sinuses through the arachnoid villi.

As Dean (18) has pointed out, the argument that antitoxin does not reach the cells of the central nervous system because after an intravenous injection of serum it has not been found possible to demonstrate antitoxin in the cerebrospinal fluid removed from the spinal theca, is only valid if we assume that there is a system of channels which connect the subarachnoid space with the interior of the cord and brain. On the other hand, if antitoxin is able to pass from the cerebral and spinal capillaries to the nerve-cells it is a matter of little importance whether it can or can not pass to the fluid in the subarachnoid space.

With regard to the possibility of neutralizing toxin present in the cerebrospinal fluid, Ransom (3) has shown that even after large doses given intravenously or subcutaneously in animals, the presence of toxin in the cerebrospinal fluid cannot be demonstrated.

Animal experiments to determine the relative values of different routes are conflicting. Sherrington (5) injected monkeys in batches of twenty-five with 8 M.L.D. into the calf-muscles, and when symptoms had developed treated them with large doses of antitoxin by various routes. Seven out of twenty-five recovered with intravenous injection and fourteen with intrathecal.

Park and Nicoll (6), working with guinea-pigs, concluded that the intraspinal route was definitely superior to the intravenous. Permin (2), with goats, could find no difference between the two routes. Gottlieb and Freund (7), with rabbits, found the intrathecal route superior.

Florey and Fildes (8) compared the two routes in rabbits. In order to be certain that the antitoxin passed out into the nervous tissue and not through the arachnoid villi into the venous sinuses they used a method of reversing the normal direction of flow of the cerebrospinal fluid suggested by Weed. This consisted of injecting hypertonic saline intravenously so that the fluid from the arachnoid space was sucked in around the

pericapillary spaces into the perineural spaces. Using this method they found that the intrathecal method had no advantage over the intravenous.

The opinions of clinicians also differ. Bruce (9), Nicoll (10), Ashurst (11), Ferris and Fuerth (12), Calvin and Goldberg (13) favour the intrathecal combined with intravenous, intramuscular, and subcutaneous routes. Yodh (14) concludes that intrathecal, by cisternal puncture, combined with intravenous and intramuscular is superior to intrathecal by lumbar puncture combined with intravenous and intramuscular. He has treated a large series of cases by each of these two combinations, but does not give exact details of incubation periods and excludes very severe cases from his series. Wainwright (15) holds that intrathecal injections are harmful and increase the mortality rate and relies on the intravenous route. Freedlander (16) obtained good results with repeated intravenous injections. Paterson (17) obtained nineteen recoveries out of twenty-six cases in children, using very large doses chiefly by the intravenous route combined with smaller doses intramuscularly. Dean (18) favours the intravenous route.

Tetanus is such a variable disease that it is very difficult to compare clinically the results of two different routes, and this does not appear to have been done satisfactorily. Most observers have used more than one route in each case or confined themselves entirely to one in a series.

From theoretical and experimental considerations the intravenous route would appear to have most in its favour, for it is clearly the most rapid way of bringing antitoxin into the general circulation and probably also of bringing it in contact with nerve-cells. The intrathecal route is a less rapid way of sending antitoxin into the general circulation and can only be more efficient if it can affect antitoxin in the central nervous system. There is little evidence that this is the case. Intrathecal injection, on the other hand, has several disadvantages: lumbar puncture must to some degree irritate the nervous system, and to perform it in tetanus a general anaesthetic is necessary. In order to give sufficient antitoxin a large amount of cerebrospinal fluid must be withdrawn. The injection of serum into the cerebrospinal fluid is liable to cause a serous meningitis within a few days to some weeks after the injection, and if this occurs when the symptoms of tetanus are still present it may cause an exacerbation which is serious. These objections also apply to the cisternal route.

In the present series, although some antitoxin was given by all routes in the earlier cases, this practice has gradually been abandoned and there has certainly been no indication that anything has been lost by this. In the last twelve cases antitoxin has been given in large doses by the intravenous route as soon as possible after admission, usually 200,000 units, the aim being to get as much antitoxin in the circulating blood as soon as possible to neutralize the toxin which is still present.

This dose of antitoxin has been given in one dose undiluted and usually without an anaesthetic. Inquiry is made as to whether the patient has had previous doses of horse serum. In one case slight collapse developed a few

minutes after the serum had been given, but this was quickly relieved by 5 minims of adrenalin. In two other cases there were slight serum rashes within ten days. Apart from these no reactions have followed the giving of serum.

The next question to be considered is whether repeated doses of serum should be given after the large initial dose. The practice of most writers appears to be to give repeated doses of serum daily or at intervals of a few days until the disease has practically subsided. This would appear to be a rational procedure in cases in which the wound cannot be properly cleaned and toxin may still be passing into the circulation. The desirability of giving repeated doses also depends on the fate of the antitoxin originally injected. If this disappears rapidly it is clearly more important to give repeated doses than if it continues to circulate. Dean's (18) evidence on this point suggests that injected antitoxin continues to circulate for a considerable period after injection, but no actual figures showing the rate of disappearance appear to be available. The fate of injected antitoxin was therefore investigated by Spooner in four cases who had each been given a single initial dose of 200,000 units. The details and results of this investigation follow, but in brief they indicate that seven days after injection there are over 10 units of antitoxin per c.c., that is a total of 50,000 units still left in the circulating blood, and at the end of fourteen days between 3 and 5 units per c.c. (see Diagram, p. 310). As a prophylactic dose of 1,500 units is sufficient to protect in most cases, even from a severe and badly contaminated wound, the possibility of gaining any advantage from a further injection of antitoxin before the tenth day appears to be doubtful. In this series the practice of giving repeated doses of antitoxin was abandoned after the first nine cases in favour of one single large dose given as early as possible.

Treatment of the wound. It is important that this shall not be attempted until antitoxin has been given because disturbance of the wound may cause a flood of toxin to be discharged into the circulation. Exacerbations of the disease have followed operation on a healed wound, and the disease has even been known to develop after operation on old war wounds for the removal of a foreign body, probably by stirring up and releasing infection pent up in an old scar. Because of these considerations care has been taken to do nothing to disturb any wound for at least an hour after the intravenous injection has been given. After this period thorough treatment of the wound is very important.

Type of wound. In most of the cases in this series the wound was comparatively trivial. Severe wounds do not often cause tetanus because in such cases prophylactic antitoxin is nearly always given. Usually, however, there is some penetration of the tissues followed by sepsis and often pus formation. Scab formation over a dirty wound is an important factor, for this leads to the formation of a septic cavity in which anaerobes can flourish. In this way even superficial abrasions may cause tetanus. The comparative

frequency of tetanus in Cambridgeshire and the surrounding counties is probably due to the fact that the soil is heavily infected and the people living on the land do not trouble to keep slight wounds clean.   The importance of scab formation in forming a cavity for anaerobes to grow in is well illustrated by Case 21.   The wound caused originally by a nail in the boot became a superficial blister.   Pus from this contained anaerobes morphologically identical with *B. tetani*.   Anaerobes were also grown from pus sealed off by a scab in Case 3 and by the thumbnail in Case 20.   A list of the wounds causing the disease in this series is given in Table IX and shows the danger of not giving prophylactic antitoxin in such cases, particularly when there is a history of contamination with earth or when from the patient's occupation such contamination is possible.

When antitoxin has been given the wounds should be treated as follows : Dirty superficial abrasions which have scabbed over should have their scabs carefully removed, and after thorough cleansing be irrigated four-hourly with hydrogen peroxide and dressed with light porous dressings which do not exclude the air.   Deep dirty wounds should as far as possible be excised and penetrating wounds opened up thoroughly and dressed in the same manner.   In very heavily infected wounds which cannot be drained, such as Case 13, satisfactory local treatment is impossible and the outlook is very bad.   Whitlows should be incised, and if the nail is involved this should be removed.   Great care should be taken to see that superficial healing does not take place.

Prevention of exhaustion and control of spasms.   Tetanus patients should be kept as quiet as possible in a darkened room.   The bedclothes should be cradled.   All necessary manipulation such as the giving of enemas should as far as possible be done while under the influence of avertin.   For the prevention of spasms, the relief of pain, and for sleep many drugs have been advocated.   Avertin was first suggested for tetanus by Momburg and Rotthaus (19).   In this series it has proved of great value given rectally in full doses as for basal anaesthesia (0·1 c.c. per kilo.), in one case for eight successive nights and in another three times in twenty-four hours.   Given in this way it will often reduce the spasms considerably or stop them entirely for several hours, reduce the rigidity and allow the patient several hours sleep.   No ill effects from its use were apparent.   Under its influence the jaw usually became relaxed, which made feeding much easier.

Paraldehyde given rectally in normal saline (1 drachm to $1\frac{1}{2}$ oz.), in doses up to 6 drachms was also valuable for sleep.   In some cases this was given by day and avertin by night and the combination appeared satisfactory.   In the present series inhalation anaesthetics have been used very little.   Gas and oxygen is preferable to chloroform or ether.   Morphia has also been used very sparingly.

Use of curare in treatment.   Curare is prepared by the natives of South America in the form of a black resinous extract from the bark of plants of the genus *Strychnos*, which they store in gourds, earthenware pots, or bamboo

sticks. A number of plants may be used in preparing the extract, and the strength of the crude preparation varies considerably in different samples. Boehm (20) found that different preparations might contain different alkaloids, most of which have a paralysing action and are typified by curarine. Their action is similar to that of the crude drug. One of them, however, curine, is a weaker poison and has an entirely different effect, for it acts upon the heart. The classical effect of active samples of crude curare is to paralyse voluntary movement by blocking the passage of impulses from the nerves to the muscles. The voluntary muscles are first paralysed and later the respiratory muscles, death taking place from asphyxia.

Hartridge and West (21) have used curare to control tetany in parathyroidectomized dogs. They found considerable variation of strength in different samples, and that two specimens out of seven possessed the power of removing tetany in the dog without causing paralysis. West (22) showed that one of these samples removed pathological rigidity in man without causing diminution of voluntary power. This selective action he called ' Lissive '. Seventeen cases of muscular rigidity resulting from disease of the pyramidal and extrapyramidal motor systems were treated. With doses which caused no detectable weakness or loss of power, there was considerable reduction of rigidity. He suggests that this lissive fraction, which is apparently present in some samples of curare only, may be of considerable therapeutic value if it can be standardized or isolated in a pure state.

West (23) has also attempted to classify the various constituents of curare according to their actions. He has shown that, in addition to the peripheral paralysing effect, certain curares show a convulsant action strongly resembling that of strychnine. In curares containing a convulsant, difficulty in inspiration due probably to bronchial spasm was caused in dogs. Generally speaking, curare left the respiratory mechanism undamaged until a severe degree of paralysis of the limb-muscles had set in, but the danger of respiratory embarrassment was one of the reasons for caution in the use of curarine in the human subject.

Pure tubo-curarine was found to cause classical peripheral paralysis in frogs and also in dogs. In the latter there was no trace of lissive power. In spastic patients with a pyramidal lesion it only caused relaxation by paralysis, and the relaxation obtained was not as satisfactory as that with some samples of curare.

Florey, Harding, and Fildes (24) have used curarine to control the spasms in rabbits inoculated with tetanus toxin. They found that by injections at intervals of half an hour they were able to maintain paralysis and so control the spasms and rigidity. No effects on the spasms or rigidity were evident unless paralysis was produced. Two dangers were apparent from this procedure: asphyxia from saliva passing back into the throat which could be controlled by atropine, and stoppage of the diaphragm from a

slight overdose.   To obviate the latter risk they advocate the use of a Drinker artificial respirator when required.   They suggest that with these precautions curarine might be used to control the rigidity and spasms of tetanus in man.   They point out that curarine is rapidly eliminated, so that the treatment could be quickly stopped if necessary.

The sample used in the three cases here described was supplied by Dr. J. F. Gaskell (26) and was of the 'Gourd' variety.   It was the most potent of ten samples whose paralysing power had been compared by injection into leeches.   Professor Hartridge also tested the potency of this sample for frogs and found that 0·005 mg. is the lethal dose for a frog weighing 26 grm. and that it paralyses frogs from that amount to 0·0025 mg.   West tested it on parathyroidectomized dogs and found it to be moderately 'lissive'.   Doses up to 32 mg. had been given to a patient with pyramidal rigidity, and this observation formed the basis of dosage in these cases.

The most marked effect observed in these three cases was to lessen the frequency and severity of the reflex spasms.   In addition there was reduction of the tonic rigidity of the masseters, back, abdominal, and limb muscles.   Some degree of the weakness of the limbs appeared to be produced, but there was never complete paralysis.   These effects were most clearly shown in Case 18 which was of intense severity with incubation period forty-eight hours.   Treatment with curare was begun when rigidity was continuous and spasms of intense severity occurring every thirty seconds : curare checked the spasms, stopped the reflex excitability, and made the rigidity very much less.   Before treatment was begun very severe spasms were induced by attempting to suck fluid, or even by the sight of fluid, and swallowing was impossible.   Improvement was first noticed ten minutes after beginning treatment, and after forty minutes when 45 mg. had been given the reflex spasms were almost completely controlled, the rigidity of the abdomen had disappeared, and the patient could drink fluid without having any spasm.   But for occasional slight spasms this condition persisted till death eight hours later.   Some weakness of the limb was produced but there was no paralysis.   Slight respiratory difficulty occurred one hour after the last injection, but apart from this the respiration did not appear to be affected.   It is important to note that hyperpyrexia (108°) occurred before death although the spasms had been almost completely controlled.

The course of the disease in Case 15 was remarkable.   It is noteworthy that although the reflex spasms grew steadily less after curare treatment had been begun and the patient appeared better, the pulse-rate continued to rise. When the reflex spasms had almost stopped twenty-four hours before death there was a sudden rise of temperature to 104°, and an increase in respiratory rate.   This may have been due to a terminal infection such as pneumonia, though there were no signs of this.   An alternative explanation is that although the spasms had been controlled by curare, tetanus toxin was

still diffusing into the nervous system and finally affected the respiratory centre and the heat regulation, and caused death. The effect may be similar but slower to that obtained in Case 18.

These cases show that the sample of curare used has the power of lessening the reflex spasms and rigidity of tetanus without causing complete paralysis of the voluntary muscles or embarrassing respiration. Such an action may be of value in helping the patient through the worst period when spasms are most severe, and so turn the balance in favour of recovery. It is possible that this action may have been the deciding factor which led to recovery in Case 10. Using curare or its alkaloids in this way it may be possible to save patients with incubation periods between four and seven days who would otherwise die. It is unlikely, however, that it will have any influence on more severe cases of the fourth degree in which the toxin has diffused very deeply into the nervous system. In Case 18 the reflex spasms were almost completely controlled, but the disease progressed ruthlessly to hyperpyrexia and death.

The difficulties of using the drug until it has been more accurately standardized are clear. Until this has been done it should be emphasized that treatment is experimental, and its use should be reserved for those cases of tetanus which will almost certainly die without further assistance. If the 'lissive' fraction which West has described could be isolated and standardized, it would probably have advantages over pure curarine in controlling the dangerous reflex spasms. How the lissive agent in curare acts is not known. The action does not appear to be peripheral. Its selective action on the reflex spasms of tetanus suggests that it may be upon the central synapses.

Feeding. An attack of tetanus means prolonged physical exertion without rest or relaxation. This is carried out involuntarily and is combined with the most severe suffering, while throughout the illness a condition of toxaemia is present. To pass successfully through such an ordeal a great deal of food is clearly of vital importance to the patient.

In an adult patient an attempt should be made to give at least two thousand calories daily. Every case of tetanus should have a special nurse, and her main duty is to see that as much food as possible is given. Glucose lemonade and egg and milk are satisfactory foods, and these should be given hourly, or more often if the patient is taking food well. Usually tetanus patients are very thirsty and will take fluids well. If trismus is severe removal of teeth may be necessary. Avertin was found to be valuable in relaxing the jaw and so making feeding easier. In Case 17 the spasm of the masseters was so severe that feeding was impossible. Under avertin, however, the jaws relaxed, so that it was possible to pass a stomach tube, which was left *in situ* so that the patient could be fed. When the muscles of deglutition are early affected, feeding becomes almost impossible by any other means, and the outlook is correspondingly bad. Rectal feeding has been used in some cases, and patients seem to retain fluids well, but it is quite

impossible in a severe case to give sufficient nourishment by this means alone.   Curare also appeared to be of value in relaxing the jaws and making feeding and swallowing easier.

The importance of giving sufficient food can hardly be over-emphasized, and success depends largely on nursing efficiency.

Prognosis and results.   It is now well known that the severity of a case of tetanus usually depends on the severity of the wound and is inversely pro-portional to the length of the incubation period.   The prognosis is worse in the aged or the physically unfit.

The results of this series are epitomized in Table VIII.

' Incubation period ' is the time of the receipt of the wound to the first symptom of the disease.   The ' Period of onset ' is the time from the appearance of the first symptom to the occurrence of the first regular generalized reflex spasms.

Only those cases in which the wound could be freely and thoroughly drained or in which the wound was short lived.   See Table IX.

All cases in which the wound was severe died.

All cases over 60 died.   (3.)

Excluding patients over 60 (leaving 18) ; only one patient with an incuba-tion period of less than seven days recovered.   (Case 9.)

All patients with an incubation period of seven days or longer recovered. (Case 21 is a possible exception to this.)

Only two patients with a period of onset of less than three days recovered. (Cases 8 and 10 each with an incubation period of two days.   It is significant that Case 8 had a prophylactic injection of 500 units of antitoxin thirty-six hours before the first symptom of the disease came on.   Case 10 was treated with curare.)

All patients who died with one exception (Case 15) had a period of onset of two days or less.   The exception had a ' period of onset ' of three days but an incubation period of four days.

The combined ' incubation period ' and ' period of onset ' was eight days or more in all those patients who recovered.   The same period was never more than seven days in those that died.   Case 17 is a possible exception to this as the incubation period could not be measured.

These observations (with Tables VIII and IX) show that for this series of cases treated in the manner described, there is a certain incubation period and a certain period of onset which is quite sharply defined and divides those cases which will die from those which will recover.   The period from the date of the injury to the appearance of the first spasm (incubation period and period of onset combined) was eight days or more in all those patients that re-covered.   The same period was never more than seven days in those that died.   If a larger series of cases were available there would be more variation in these figures, and indeed reference to the records of published cases show that some exceptions can be found.

The fact that the probability of survival can be narrowed down and ex-

pressed numerically, even if the figures are open to fallacies, is very important and should be made use of in assessing the results of any new method of treatment such as curare.   Tetanus is such a variable disease that the general percentage of recoveries in any given series of cases may give quite a false impression of the value of the methods of treatment employed.   A method more likely to give reliable results would be to consider the effects of treatment on patients with an incubation period of six days or less and a period of onset of two days or less, or with combined periods of eight days. Thus in the present series one patient with an incubation periods of eight days, four with periods of seven and one with a period of five recovered, and three of these had combined incubation periods and periods of onset of eight or nine days.   It is these patients whose lives may have been saved by treatment.   The remainder of those who survived might have done so without treatment, and of those who died it is probable that only one (Case 14) had any chance of being influenced by any methods of treatment known.

Summary of results.   Of twenty-one cases eleven recovered.   Recovery rate : 54·5 per cent.

This recovery rate is poor compared with many other series published. In comparing them, however, it must be remembered that three of the patients who died were over 60, and of the remainder, one had an incubation period of five days, three of four, and one of two.   In one other, in which the incubation period could not be measured, the period of onset was thirty-four hours.

It is interesting to compare this series with that of Paterson, whose recovery rate is very high, nineteen patients recovering out of twenty-six. Recovery rate 73 per cent.   He, however, was treating entirely children, and had no case with an incubation period of less than six days.

The Rate of Disappearance of Tetanus Antitoxin from the Blood of Four Cases of Tetanus treated by the Intravenous Injection of a Single Dose of 200,000 International Units of Antitoxin

In 1917 Dean (18) showed that considerable amounts of antitoxin persisted in the blood for at least a month after the intravenous injection of one dose of 30,000 units.   In the investigation here reported, the disappearance of antitoxin has been followed after the intravenous injection of a larger dose, 200,000 units.   Blood samples were collected for examination from four such cases, at intervals during periods of thirty-two, twenty-eight, thirty-two, and sixty-three days respectively after the injection of antitoxin.

The object of the investigation was to detect the persistence in the blood of relatively large amounts of antitoxin, which might be of curative significance.   For this purpose an exact titration of the number of antitoxic units per c.c. was not considered necessary.   The accurate titration of one sample requires the use of large numbers of animals, and a proper consideration

of the 'characteristic' of the toxin used. (Trevan (27); quoted by Top-ley (28).)

It was thought to be sufficient for the present purpose to use a test dose of toxin containing 100 average lethal doses for the guinea-pigs used, and to rely on two titrations, a rough one and a finer one, for each serum. The rough titration was carried out on three or four guinea-pigs, using one guinea-pig only for each serum dilution: the finer titration also involved three or four guinea-pigs, and again only one animal was used for each serum dilution, but the range of dilutions used was smaller.

The results of finer titrations alone have been recorded in the tables and diagram; they were always consistent with the results of the preliminary titrations.

Each result, therefore, depends on the death or survival of one guinea-pig. With each test there was included one guinea-pig, which received 1/100th of the test dose of toxin, without any serum. Table I, which shows the fates of all these control guinea-pigs, indicates that the test dose of toxin was fairly uniform, and that it did contain about 100 average lethal doses.

While it is admitted that the titration of a single serum by such a method, involving the death or survival of only one animal for each serum dilution, is open to criticism, yet it is felt that in a series such as the present one, in which blood samples from the same patient were compared with one another at intervals of a few days, the value obtained for any one sample of serum gains in significance from the values obtained for the other sera in the series, especially if these values indicate a regular change in the antitoxic content of the patient's blood.

The tables and diagrams show that in these four cases the rate of dis-appearance of antitoxin followed a fairly regular course, over 10 units per c.c. remaining after seven days and between 3 and 5 after fourteen days, and that in three cases as late as one month after the injection of 200,000 units, there still remained about one unit of antitoxin per c.c. of serum.

This latter result is in accord with those of Dean (1917), who found appreciable quantities of antitoxin in the sera of eight cases as late as twenty, thirty, and even thirty-nine days after the injection of a single dose of 30,000 units intravenously.

Method. Sera were stored, after separation from the clot, in the cold room at about 4° C., without being heated and without the addition of any preservative. They were unavoidably kept for different times before their final titration, the delay varying from a few days to two months. A stable glycerinated tetanus toxin was kindly supplied by Dr. G. F. Petrie of the Lister Institute.

Preliminary tests and an analysis of the controls indicate that 1/5000 c.c. of this toxin killed the guinea-pigs used on the average in 3·5 days (Table I). A uniform dose of 1/50 c.c. (0·5 c.c. of a dilution of 1/25) was used throughout the titrations as a Test Dose.

At the end of the investigation the toxin which had been used throughout was roughly compared with a fresh batch of the same toxin against the Lister standard antitoxin, both kindly provided by Dr. Petrie. Table II indicates that little change has occurred in the toxin in the two years over which the work extended, and that the Test Dose was about equivalent to 1/10 unit of antitoxin. 1·0 c.c. of an appropriate dilution of each serum was mixed with 1·0 c.c. of toxin 1/25. The mixture was allowed to stand for half an hour at room temperature, and then 1·0 c.c. was injected into the quadriceps extensor muscles of the right fore limb of a guinea-pig weighing between 300 and 400 grm.

The toxin 1/25 was further diluted to a final dilution of 1/5000, and 1·0 c.c. of this was injected into a control guinea-pig.

The animals were examined daily and their condition noted.

TABLE I

Analysis of Control Guinea-pigs

Date.	Weight of guinea-pig.	Day of death.
	grm.	
30.11.32	330	4
5.12.32	350	5
7.12.32	350	Survived. (This group was disregarded)
10.12.32	400	4
10.12.32	320	4
11.12.32	420	3
13.12.32	330–50	3
14.12.32	330	4
16.12.32	320	3
5.1.33	350–65	2
10.1.33	350	2
10.2.33	350	2
15.2.33	370	3
13.3.33	350	3
21.3.33	350	3
24.3.33	—	3
18.4.33	330	3
25.4.33	335	3
1.5.33	—	2
24.11.33	360	4
1.12.33	300	4
5.12.33	300	5
13.12.33	300	3
16.12.33	330	3
10.1.34	350–70	Survived. (This group was disregarded)
22.2.34	—	4
7.3.34	400	4
15.3.34	370	4
20.3.34	360	4
21.3.34	270	4

The inoculum in each case was 1·0 c.c. of toxin 1/5000.

Died on the 2nd day 4   Died on the 5th day 2
,, ,, 3rd ,, 11   Survived the 5th day 2
,, ,, 4th ,, 11

TABLE II

Titration of Old and New Toxins against Lister Standard Antitoxin

(1/92 c.c. of serum contains 1/5 international units)

Guinea-pig.		Toxin.	Antitoxin c.c.	Day of death.	State on 4th day.
No.	Weight. grm.				
1	300	Old	1/500	3	—
2	350	,,	1/500	4	—
3	360	,,	1/450	5	Arm rigid
4	320	,,	1/450	4	,,
5	330	,,	1/425	5	,,
6	350	,,	1/425	5	,,
7	280	,,	1/384	Survived	Normal
8	300	,,	1/384	7	,,
9	300	,,	1/288	Survived	,,
10	280	,,	1/288	Survived	,,
11	300	New	1/500	4	—
12	310	,,	1/500	4	—
13	330	,,	1/450	4	—
14	330	,,	1/450	4	—
15	350	,,	1/425	3	—
16	300	,,	1/425	4	—
17	280	,,	1/384	7	Normal
18	300	,,	1/384	7	,,
19	300	,,	1/288	Survived	,,
20	280	,,	1/288	Survived	,,

The test dose of toxin was in each case 1/50 c.c.   The old toxin was used in the titration of all sera from patients ; the new toxin, received at the end of the investigation, is shown for comparison, and to demonstrate that the toxin used for titration of sera had not deteriorated significantly in the course of the experiments.

TABLE III

Case 1. 200,000 units of antitoxin given 13.11.32.

Serum.	Date.	Day.	Weight of guinea-pig in grm.	c.c. of serum.	Day of death.	State of guinea-pig on 4th day.
1	16.11.32	3	330–50	0·004	—	Normal
			330–50	0.002	8	,,
			350	0·001	3	—
			350	0·0001	2	—
2	18.11.32	5	330–50	0·004	—	Normal
			330–50	0.002	4	—
3	21.11.32	8	330–50	0·008	—	Normal
			330–50	0·004	4	—
4	22.11.32	9	370	0·01	—	Normal
			320	0·005	3	—
5	25.11.32	12	370	0·02	—	Normal
			350	0·01	4	—
6	28.11.32	15	320	0·03	—	Normal
			320	0·02	—	Arm stiff
7	7.12.32	24	320	0·08	—	Normal
			320	0·06	10	,,
			320	0·04	4	—
			320	0·02	2	—
8	15.12.32	32	320	0·03	—	Normal
			?	0·02	9	Arm rigid

TABLE IV

Case 2. 200,000 units of antitoxin given 6.3.33.

Serum.	Date.	Day.	Weight of guinea-pigs in grm.	c.c. of serum.	Day of death.	State of guinea-pig on 4th day.
1	10.3.33	4	350	0·01	—	Normal
			350	0·005	7	No rigidity
			350	0·005	—	Arm rigid recovered
			350	0·004	4	—
			350	0·003	3	—
2	20.3.33	14	350	0·04	—	Normal
			350	0·02	—	Arm slightly stiff
			350	0·01	3	—
3	3.4.33	28	?	0·08	—	Normal
			?	0·06	5	Rigid and curved back
			335	0·06	6	Rigid and curved back
			335	0·05	4	—

TABLE V

Case 3. 200,000 units of antitoxin given 6.11.33.

Serum.	Date.	Day.	Weight of guinea-pig in grm.	c.c. of serum.	Day of death.	State of guinea-pig on 4th day.
1	8.11.33	2	380	0·0025	—	Normal
			280	0·002	6	Arm stiff
			300	0·0015	3	—
			300	0·001	2	—
2	16.11.33	10	310	0·007	—	Arm stiff recovered
			300	0·005	3	—
3	22.11.33	16	370	0·016	—	Normal
			350–70	0·015	—	,,
			270	0·015	8	Arm stiff
			350	0·013	—	Arm slightly stiff
			350–70	0·01	4	—
4	24.11.33	18	350–70	0·015	—	Normal
			300	0·015	—	Arm stiff
			350–70	0·01	3	—
5	8.12.33	32	320	0·06	—	Normal
			330	0·04	—	,,
			340	0·03	4	—
			400	0·02	2	—

TABLE VI

Case 4. 200,000 units of antitoxin given 23.1.34.

Serum.	Date.	Day.	Weight of guinea-pig in grm.	c.c. of serum.	Day of death.	State of guinea-pig on 4th day.
1	6.2.34	13	320	0·03	—	Normal
			330	0·025	9	Arm slightly stiff
			370	0·02	7	Rigid and curved
			?	0·02	4	—
			?	0·015	4	—
2	15.2.34	22	420	0·3	—	Normal
			320	0·2	5	Arm rigid
			400	0·1	2	—
3	6.3.34	41	350	0·5*	4	—
			400	0·5	2	—
4	28.3.34	63	250	0·5*	2	—

* These two guinea-pigs received half a test dose of toxin only, i.e. 0·5 c.c. of 1/50.

1st. Case
2nd. Case
3rd. Case
4th. Case

Int. Units per C.C.

Days after intravenous injection of 200,000 international units
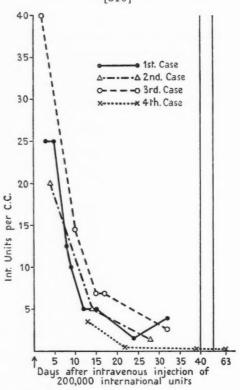
TABLE VII. *Summary of the Four Cases*

Case.	Serum.	Day.	c.c. of serum neutralizing 1 test dose of toxin.	No. of test. Doses of toxin neutralized by 1·0 c.c. of serum.	International units per c.c. of serum (approximately).
1	1	3	0·004	250	25
	2	5	0·004	250	25
	3	8	0·008	125	12·5
	4	9	0·01	100	10
	5	12	0·02	50	5
	6	15	0·02	50	5
	7	24	0·08	12·5	1·25
	8	32	0·03	33·3	3·33
2	1	4	0·005	200	20
	2	14	0·02	50	5
	3	28	0·08	12·5	1·25
3	1	2	0·0025	400	40
	2	10	0·007	143	14·3
	3	16	0·015	67	6·7
	4	18	0·015	67	6·7
	5	32	0·04	25	2·5
4	1	13	0·03	33·3	3·33
	2	22	0·3	3·3	0·33
	3	41	>1·0	<1·0	0·1
	4	63	>1·0	<1·0	0·1

All readings in this table are taken from guinea-pigs which survived. These results are embodied in the diagram.

Summary

The treatment of tetanus is discussed and the results obtained in twenty-one cases are analysed.

The rate of disappearance of injected antitoxin has been investigated in four cases after the injection of a single dose of 200,000 units intravenously. It has been shown that antitoxin disappears from the blood of these patients rapidly at first and more slowly later, and that seven days after the injection about 10 units per c.c. and at the end of fourteen days between 3 and 5 units per c.c. remained.

It is suggested that routine treatment should include a single dose of 200,000 units of antitoxin given intravenously as early as possible and followed after an interval by thorough treatment of the wound. As liberal a diet as possible should be given and an attempt made to give over 2,000 calories per day. The value of avertin in controlling the spasms and giving sleep is emphasized.

The effects of treatment of three cases with a moderately ' lissive ' sample of curare are described and the possibilities of this treatment are discussed.

The prognosis is considered in relation to incubation period and ' Period of onset '. These two factors should be given greater consideration in assessing results and in choosing cases for any new method of treatment such as curare.

TABLE VIII

Summary of Cases

Case No.	Age.	Sex.	Incubation period.	Period of onset.	Duration of spasms.	Dose* A.T.S.	Result.
1	23	M	? (Long)	12 Days	None	$2\frac{1}{2}$	Recovered
2	11	M	16	5 ,,	8 Days	$3\frac{1}{2}$	,,
3	11	M	11	3 ,,	5 ,,	$2\frac{1}{2}$	,,
4	10	M	9	5 ,,	6 ,,	$3\frac{1}{2}$	,,
5	3	F	?	4 ,,	10 ,,	1	,,
6	11	M	8	3 ,,	7 ,,	2	,,
7	19	F	7	5 ,,	6 ,,	3	,,
8	18	M	7	5 ,,	5 ,,	2	,,
9	19	M	7	2 ,,	6 ,,	2	,,
10	39	M	7	2 ,,	12 ,,	2	,,
11	41	M	5	3 ,,	10 ,,	$2\frac{1}{2}$	,,
12	12	M	6	18 Hours	1 ,,	$3\frac{1}{2}$	Died
13	10	M	5	2 Days	1 ,,	$5\frac{1}{2}$	,,
14	11	M	4	2 ,,	3 ,,	2	,,
15	31	M	4	3 ,,	4 ,,	2	,,
16	3	M	? 4	$1\frac{1}{2}$,,	1 ,,	1	,,
17	51	M	?	34 Hours	30 Hours	2	,,
18	7	M	2	1 Day	18 ,,	1	,,
19	68	M	12	$1\frac{1}{2}$ Days	1 Days	2	,,
20	60	M	10	2 ,,	2 ,,	1	,,
21	73	M	10	$1\frac{1}{2}$,,	3 ,,	1	,,

* In 100,000 units (Int.).

TABLE IX

Case No.	Type of wound.	Result.
1	No wound found	Recovered
2	Thorn in leg. Pus	,,
3	Splinter in leg. Sepsis	,,
4	Abrasion. Foot. Scab	,,
5	Abrasions, legs, knees, and hands	,,
6	Graze left knee. Scab. Pus formation	,,
7	Pin-prick. Little finger. Subcuticular. Whitlow	,,
8	Slight penetrating wound. Heel. Sepsis and Scab	,,
9	Rusty nail in sole	,,
10	Finger cut with reed	,,
11	Crushed finger on cart-wheel. Stitched up	,,
12	Septic cut left knee. 3 in. long, 1 in. deep	Died
13	Compound fracture radius and ulna from fall on barn floor	,,
14	Lacerated dirty cut left thigh. 2 in. long, $\frac{1}{2}$ in. deep	,,
15	Boil on neck. Slight scratches on hands	,,
16	Ear discharge. 4 days	,,
17	Whitlow of finger	,,
18	Abrasions left elbow, knees and right heel	,,
19	Back of both hands scratched with rusty nails	,,
20	Whitlow of thumb (Gardener)	,,
21	Nail run in big toe. Septic blister	,,

Description of Cases [2]

Case 1. Male, aged 23, horsekeeper. No history of injury. Stiffness of the jaw and back came on fourteen days before admission and gradually became worse.

State on admission. Muscles of chest, neck, and abdomen in a state of tonic rigidity. Trismus and risus sardonicus present. Profuse sweating.

Treatment and progress. 40,000 units intrathecally and the same amount intravenously on admission. 160,000 units by various routes during the next six days. During the course of the illness there were no clonic reflex spasms. The rigidity and trismus gradually passed off, and the patient was discharged well sixteen days after admission.

Case 2. Male, aged 11. Wound with thorn below right knee twenty-one days before admission. Sixteen days later he felt ill, could not eat, and bit his tongue, and later could not open his mouth.

State on admission. Severe tonic rigidity of neck, chest, and abdomen. Trismus and risus sardonicus present. Clonic reflex spasms with opisthotonos every five minutes or on stimulation. (These began the day of admission.)

Treatment and progress. 80,000 units intravenously, 40,000 intramuscularly, and 40,000 round wound were given. Wound then treated. 1 c.c. pus and thorn beneath scab. Four days later a further 80,000 were given intravenously and 120,000 intramuscularly. Reflex spasms persisted for six days and rigidity for fourteen days after admission.

Result. Recovery. Anaerobic organisms grown from pus.

[2] Ten of these cases have been published in the *Brit. Med. Journ.*, 1932, 1.

Case 3. Male, aged 11. Wound with splinter of wood below left knee fourteen days before admission. Treated by doctor and healed normally. Eleven days later the left leg, then the right leg, and then the jaw became stiff.

State on admission. Tonic rigidity of neck, spine, and abdomen. Trismus. Could not speak or swallow fluids. Severe reflex spasms with opisthotonos every half-hour.

Treatment and progress. 70,000 units intrathecally, 60,000 intramuscularly, and 30,000 intravenously on admission. 148,000 units by various routes during the next six days. Reflex spasms lasted six days and tonic rigidity ten days after admission.

Result. Recovery.

Case 4. Male, aged 10. Fourteen days before admission noticed to be limping. Nine days later pain and stiffness in back and neck followed by increasing stiffness of the jaw.

State on admission. Tonic rigidity of neck, back, chest, and abdomen. Trismus and risus sardonicus. Occasional reflex spasms. Scabs on right foot.

Treatment and progress. 40,000 units intravenously and the same amount intrathecally on admission. These amounts repeated on the following day. 180,000 were given by various routes during the next ten days. Reflex spasms lasted five days and rigidity three weeks after admission.

Result. Recovery.

Case 5. Female, aged 3. Double otitis media at two months. At 2 p.m. the day before admission she fell down and grazed her knees, legs, and hands, and bruised her forehead. Following this she was fretful and at midnight lost consciousness for ten minutes. During this attack she became rigid and blue, her teeth were clenched, and she foamed at the mouth. After the attack the right side of the face was noticed to be weak and the jaw was stiff.

State on admission (twenty-four hours after fall). Back arched and rigid, jaw stiff. Ptosis of right eye and right facial weakness. No ear discharge. Cerebrospinal fluid normal.

Progress and treatment. Rigidity and trismus increased. Three days after admission another fit occurred with opisthotonos and cyanosis, and after this further fits with increasing frequency. At the worst period reflex tetanic spasms occurred every five minutes and lasted for thirty seconds. They finally ceased twelve days after admission. The tonic rigidity gradually passed off and had disappeared twenty-six days after admission. 100,000 units were given intravenously five days after admission.

Result. Recovery.

Case 6. Male, aged 11. Ten days before admission fell off bicycle and grazed knee. Iodine applied. Eight days later he had pain in the stomach and back and could not open his mouth.

State on admission. Tonic rigidity of neck, back, and abdomen. Risus sardonicus and trismus.

Progress and treatment. 200,000 units intravenously on admission. Wound treated. Pus beneath scab. Reflex spasms first occurred the day after admission. These persisted three days. Tonic rigidity persisted for sixteen days.

Result. Recovery.

Case 7. Female, aged 19. Domestic servant. Twelve days before admission she pricked her finger with a pin on her dress. Seven days later she had pain and stiffness in the neck, shoulders, and chest. The next day she could not open her mouth. Severe spasms first occurred the night before admission.

State on admission. Severe tonic rigidity of neck, spine, chest, and abdomen. Trismus and risus sardonicus. Profuse sweating. Subcuticular whitlow of little finger. Severe reflex spasms with opisthotonos every fifteen minutes.

Progress and treatment. 140,000 units intravenously and 60,000 intramuscularly on admission. 100,000 intravenously the following day. Reflex spasms lasted four days and tonic rigidity three weeks.

Result. Recovery.

Case 8. Male, aged 18. Cement worker. Ten days before admission penetrating wound of right heel. Seven days later pain in back followed by stiffness of jaw.

State on admission. Tonic rigidity of chest, spine, and abdomen. Trismus.

Progress and treatment. 200,000 units intravenously. Reflex spasms first occurred two days after admission. Two-hourly at first and later every fifteen minutes. These lasted five days. The tonic rigidity persisted for nineteen days.

Result. Recovery.

Case 9. Male, aged 19. Labourer. Seven days before admission he ran a rusty nail into the sole of his right foot. Five days later 500 units of antitoxin were given by his doctor. On the day of admission he noticed stiffness of jaw, twitching of the right leg and pain in the back and neck.

State on admission. Tonic rigidity of neck, back, and abdomen. Trismus.

Progress and treatment. 200,000 units intravenously. Reflex spasms first occurred the day after admission. These persisted for seven days and at their worst occurred every ten minutes. The tonic rigidity lasted for eighteen days.

Result. Recovery.

Case 10.[3] Male, aged 39. Labourer. In the afternoon of Jan. 15 he cut the tip of the second finger of the left hand deeply on a reed. He treated it by soaking it daily in hot water. On Jan. 22 his jaw was stiff and he had difficulty in swallowing. These symptoms grew worse and he was admitted on the 24th.

State on admission. Trismus. Risus sardonicus. Tonic rigidity of spine, chest, and abdomen. Severe reflex spasms every ten minutes. Whitlow of finger fluctuant and full of pus. No teeth in upper jaw.

Progress and treatment. 200,000 units intravenously and 2,000 subcutaneously into the infected finger. Half an hour later the whitlow was incised and washed out with hydrogen peroxide. No further antitoxin was given.

Progress. Reflex spasms began shortly after admission and increased rapidly in severity. By the evening the patient was having severe spasms which were brought on by the slightest sound or movement, and these

---

[3] Cases 10 and 18 have been published in the *Lancet*, 1934, ii. 475.

occurred every minute or so. Opisthotonos occurred during the spasms, the back was rigid and arched between spasms, and the abdomen board-like.

The sedatives used during the course of the illness were avertin and paraldehyde given rectally, and occasional small doses of morphia. 7.3 c.c. of avertin (full dose for basal anaesthesia) was given every night for eight nights. From three to six drachms of paraldehyde were given rectally, dissolved in normal saline, every day for ten days. Food in the form of glucose, lemonade, milk, and egg and milk were given hourly when the patient was awake. The fact that there were no teeth in the upper jaw made feeding a good deal easier.

By Jan. 26, however, the reflex spasms were getting more frequent and severe, and the patient was showing signs of exhaustion. Treatment with curare was therefore begun. Four doses of 32 mg. were given subcutaneously at six-hourly intervals beginning at midday on the 26th. Within two hours of starting this treatment the reflex spasms were less severe, the tonic rigidity of the arms and abdomen was less, and the spasm of the masseters was less, so that feeding was made a good deal easier. The patient had less pain and was more comfortable. He complained of no abnormal sensations after injection and there was no evidence at any time of difficulty in breathing. The pulse-rate, however, continued to rise. Observations on the blood-pressure and reflexes could not be made. This improvement continued for forty-eight hours, but on the 29th reflex spasms and rigidity began to get worse again. He was therefore given three more injections of 32 mg. of curare at six-hourly intervals. Following this, the same effects were observed and the same improvement occurred, but the pulse-rate still remained rapid. On Feb. 1 spasms and rigidity again began to get worse, and so one more injection of 32 mg. was given. Following this there was steady improvement and the spasms gradually became less and less and ceased on Feb. 6. The tonic rigidity of the abdomen and back and the opisthotonos gradually passed off and had disappeared by Feb. 17. No abnormal symptoms were observed during convalescence, but the wasting and weakness of the forearms and legs were very marked. Before discharge on Feb. 28 the patient could walk about the ward and the central nervous system showed no abnormality. One month later he was perfectly well but for some weakness of the arms and legs.

Case 11. Male, aged 41. Labourer. Little finger of left hand crushed on wheel of pony trap five days before admission. A slit up the finger was sutured by the doctor who attended him at the time of the accident. Four days later his throat felt 'sore', and on the day of admission he complained of stiffness of the jaw, difficulty in swallowing, and a tightness across the chest.

State on admission. Tonic rigidity of neck, spine, and abdomen. Trismus. Risus sardonicus.

Progress and treatment. 200,000 units intravenously and 20,000 subcutaneously into the infected finger.

The tonic rigidity increased and the difficulty in swallowing grew greater. Reflex spasms first occurred three days after admission, and lasted ten days. At their worst they occurred every ten minutes. The tonic rigidity persisted twenty-one days. A further 40,000 units was given intravenously on the fourth and again on the fifth day after admission.

Result. Recovery.

Case 12. Male, aged 12. Deep and dirty cut on the knee due to a fall on the road, seven days before admission. This was stitched up at the time of the accident but no antitoxin was given. Eighteen hours before admission he complained of pain and stiffness in the left leg which spread rapidly to the muscles of the back, neck, and jaw.

State on admission. Severe tonic rigidity and trismus with reflex spasms of great severity every few minutes.

Treatment and progress. 140,000 units intravenously on admission and a further 220,000 by various routes during the next eight hours. Death took place twelve hours after admission.

Case 13. Male, aged 10. Wound. Compound fracture of radius and ulna seven days before admission. Five days later he complained of pain in the back. Severe reflex spasms began the day of admission.

State on admission. Almost continuous opisthotonos and reflex spasms of great severity. Trismus and risus sardonicus.

Progress and treatment. During the seven hours before death 520,000 units were given, 350,000 intravenously. An extensive cellulitis involved the whole arm and this could not be drained.

Case 14. Male, aged 11. Wound. Deep, dirty, lacerated wound of left thigh, seven days before admission. Three days before admission pain in the back and stiffness of the jaw began. Reflex spasms began just before admission.

State on admission. Rigidity of spine, chest, and abdomen. Trismus and risus sardonicus. Severe reflex spasms occurred hourly.

Progress and treatment. 200,000 units were given intravenously. Reflex spasms increased in severity and death took place sixty hours after admission.

Case 15. Male, aged 31. Labourer. Blow on chest boxing (skin not broken), ten days before admission. Five days later developed boil on back of neck. Two days before admission stiffness of the neck and jaws appeared.

State on admission. Tonic rigidity of neck and trunk. Trismus. Boil discharging slightly. Very slight scabs on fingers.

Progress and treatment. 200,000 units given intravenously. The boil was later incised and cleaned and all scabs were removed. Short generalized reflex spasms first began the day after admission and rapidly increased in severity. By the evening they were occurring every three minutes. Curare treatment was begun at 11 p.m. and continued as follows:

Oct. 31, 11 p.m. 32 mg.; Nov. 1, seven doses of 32 mg. given at the following times: 7 a.m., 9.30 a.m., 11.30 a.m., 2.30 p.m., 5 p.m., 8 p.m., 10 p.m. (total 256 mg. in twenty-four hours). Warmed oxygen was given with a nasal catheter for periods of ten minutes occasionally throughout the day, but there was no sign at any time of respiratory embarrassment or of any alteration of either costal or diaphragmatic breathing. The respirations remained at twenty-four except during spasms, when they increased. The pulse-rate was taken every fifteen minutes and rose steadily throughout the illness. There was no indication that the rate was affected by the curare. The curare appeared to act in about an hour, but this period was difficult to determine. During treatment with curare the reflex excitability appeared to get less, the severity and frequency of the reflex spasms became less, and the pains were less severe. No detectable weakness

of muscles or paralysis was produced and no excessive salivation. No further curare was given after 10 p.m. Nov. 1. On Nov. 2 the reflex spasms were very much less frequent and severe, and reflex excitability was less. On the 3rd spasms only occurred once or twice an hour and were very slight and caused little pain, and on the 4th had almost ceased. In the evening, however, the temperature rose to 104° suddenly and the respirations became rapid. He presented the appearance of lobar pneumonia although there were no signs of cough or pain. The pulse and respirations became steadily more rapid, and he died of cardiac failure on Nov. 5.

Case 16. Male, aged 2½. Wound. Slight superficial graze of left elbow fourteen days before admission. Ear discharge for four days before admission with 'fits' and inability to open the mouth.

State on admission. Tonic rigidity of trunk. Trismus and risus sardonicus. Profuse sweating. Very severe reflex spasms hourly.

Treatment and progress. 30,000 units intrathecally and 20,000 intramuscularly. Reflex spasms increased rapidly in frequency and severity. The rectal temperature rose to 110° before death, twenty-four hours after admission.

Case 17. Male, aged 51. Labourer. Wound. While 'pulling' sugar beet twelve days before admission he noticed that his finger was sore. This became septic. The day before admission his jaw was stiff and later there was pain in the neck and abdomen and difficulty in swallowing.

State on admission. Tonic rigidity of trunk and neck. Severe trismus. Inability to swallow. Risus sardonicus. Whitlow of left index finger.

Treatment and progress. 200,000 units intravenously on admission. Nail removed and wound cleaned later. Reflex spasms began the day of admission and were very severe (one lasted ten minutes). Trismus made feeding impossible. Death took place just three days after the first symptom.

Avertin was very useful. Each dose appeared to control the reflex spasms, lessen tonic rigidity, and relax the jaw for about four hours. The effect on the masseters enabled the patient to be fed. After three doses a stomach tube was passed and left *in situ* for feeding.

Case 18. Male, aged 7. On July 12 fell off bicycle and grazed his left elbow, knees, and right heel on the road. No treatment given. On the morning of the 14th he complained of stiffness of jaw and pain in the neck, shoulders, and the left side of the chest. These symptoms grew steadily worse.

State on admission. Severe tonic rigidity of trunk, with trismus and risus sardonicus. Occasional slight reflex spasms with opisthotonos occurred. Wounds had scabbed over.

Treatment and progress. 100,000 units of antitoxin were given intravenously and the wounds were cleaned. Rigidity and reflex spasms became more severe and frequent. At 10.30 p.m. the jaw was continuously clenched, the back arched and rigid, the abdomen board-like, and the limbs stiff. Reflex spasms of the most intense severity occurred every thirty seconds and were caused by the slightest sound or touch. The attempt to give water with a spoon brought on severe spasms, swallowing was impossible, and attempts to suck fluid through a tube had the same effect. Perspiration was profuse, temperature 104° F., and pulse-rate 140–50. At 11.30 p.m. 7·5 mg. of curare were given subcutaneously. Five minutes later the reflex

spasms were less severe, the reflex excitability was less, and the limbs were less rigid. At 11.40 7·5 mg. were given, at 11.50 15 mg., and 12.10 15 mg., with progressive improvement. After the last injection of curare the rigidity of the abdomen had disappeared between spasms, the limbs were relaxed, but not completely paralysed, the mouth could be opened, and fluid could be sucked and swallowed without bringing on spasms. Reflex excitability had almost disappeared, for the arms and legs could be manipulated freely without causing reflex spasms. Only occasional slight spasms occurred throughout the night. At 1 a.m. there was some respiratory difficulty, but this improved. The pulse, however, grew weaker and more rapid, and the temperature rose steadily to 108° F. at 5.30 a.m. The respiration then began to fail and the child died at 6.20 a.m.

Case 19. Male, aged 68. Wound. Both hands scratched with rusty nails fourteen days before admission. Twelve days later stiffness of jaw, neck, and back.

State on admission. Tonic rigidity of trunk and trismus. Marked arteriosclerosis, chronic bronchitis, and emphysema.

Progress and treatment. 200,000 units intravenously on admission. Reflex spasms first occurred the day of admission. Oedema of the lung preceded death on the following day.

Case 20. Male, aged 60. Gardener. Whitlow of thumb ten days before admission. Eight days later he developed stiffness of the jaw followed by a ' sort of fit '.

State on admission. Tonic rigidity of neck and trunk. Trismus and risus sardonicus. Reflex spasms with opisthotonos occurred every few minutes. Marked arteriosclerosis, chronic bronchitis, and emphysema.

Treatment and progress. 120,000 units intramuscularly on admission. The reflex spasms increased in severity and death occurred thirty-six hours after admission. Anaerobes grown from pus after removal of thumb nail.

Case 21. Male, aged 73. Ten days before admission he trod on a nail, wounding the big toe which became septic. On the day of admission he complained of stiffness of the jaw and pain in the back.

State on admission. Tonic rigidity of the neck and trunk muscles. Trismus and risus sardonicus. Occasional slight reflex spasms with opisthotonos. Arteriosclerosis present. Septic blister on right big toe which contained pus (1 cm.). Cultures yielded *B. tetani* and other anaerobes.
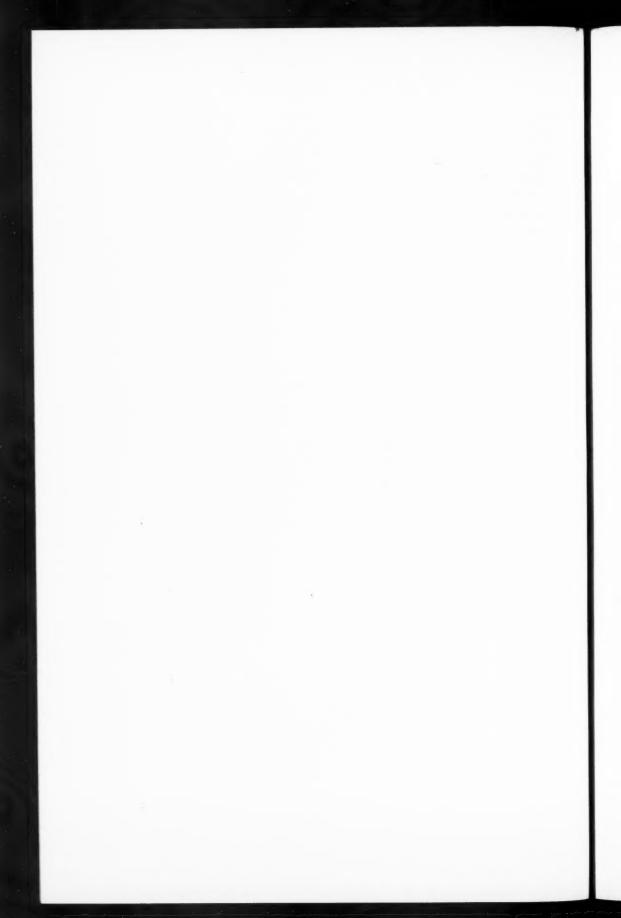
Progress and treatment. 40,000 units intrathecally and 20,000 intravenously, repeated the following day. Reflex spasms and rigidity became more severe until death, two days after admission.

REFERENCES

1. Meyer, H., and Ransom, F., *Arch. f. exp. Pathol.*, Berl., 1903, xlix. 369.
2. Permin, C., *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, Jena, 1914, xxvii. 1.
3. Ransom, F., *Lancet*, Lond., 1917, ii. 928.
4. Weed, L., *Physiol. Rev.*, Balt., 1922, ii. 171.
5. Sherrington, C. S., *Lancet*, Lond., 1917, ii. 964.
6. Park, W. H., and Nicoll, M., *Journ. Amer. Med. Assoc.*, Chicago, 1914. lxiii. 235.
7. Gottlieb, R., and Freund, H., *Münch. med. Wchnschr.*, 1916, lxiii. 741.
8. Florey, H., and Fildes, P., *Brit. Journ. Exp. Path.*, Lond., 1927, viii. 393.
9. Bruce, Sir David, *Lancet*, Lond., 1917, i. 680.
10. Nicoll, M., *Journ. Amer. Med. Assoc.*, Chicago, 1921, lxxvi. 112.
11. Ashurst, A. P. C., *ibid.*, 1926, lxxxvii. 2089.
12. Ferris, J. L., and Fuerth, A. L., *ibid.*, 1925, lxxxv. 704. (Ref.)
13. Calvin, J. K., and Goldberg, A. H., *ibid.*, 1930, xciv. 1977.
14. Yodh, B. B., *Brit. Med. Journ.*, Lond., 1932, ii. 589.
15. Wainwright, J. M., *Arch. Surg.*, Chicago, 1926, xii. 1062 ; *Journ. Amer. Med. Assoc.*, Chicago, 1926, lxxxvi. 1642.
16. Freedlander, S. O., *Ann. Surg.*, Philad., 1927, lxxxv. 405.
17. Paterson, A. E., *Med. Journ. of Australia*, New South Wales, 1930, i. 832.
18. Dean, H. R., *Lancet*, Lond., 1917, i. 673.
19. Momburg, F., and Rotthaus, E., *Deutsche med. Wchnschr.*, Leipz., 1929, xxii. 1164.
20. Boehm, R., *Arch. f. exper. Path. u. Pharm.*, Berl., 1895, xxxv. 16 ; 1908, lviii. 265 ; 1910, lxiii. 177.
21. Hartridge, H., and West, R., *Brain*, Lond., 1931, liv. 312 and 508.
22. West, R., *Proc. Roy. Soc. Med.*, Lond., 1932, xxv. 39.
23. West, R., *Lancet*, Lond., 1935, i. 88.
24. Florey, H. W., Harding, H. E., and Fildes, P., *ibid.*, 1934, ii. 1036.
25. Hunter, H., *British Guiana at the Paris Exhibition*, Lond., 1878, Preface, p. 80.
26. Gaskell, J. F., *Phil. Trans. Roy. Soc.*, B., Lond., 1914, ccv. 191.
27. Trevan, J. W., *Proc. Roy. Soc.*, B., Lond., 1927, ci. 483.
28. Topley, W. W. C., *Outline of Immunity*, Lond., 1933.

THE INCIDENCE OF INTRATHORACIC NEOPLASIA IN THE TEACHING HOSPITALS OF GREAT BRITAIN 1894–1928 [1]

By R. D. PASSEY and J. McD. HOLMES

(From the Department of Experimental Pathology and Cancer Research in the University of Leeds)

Introduction

IN the past ten years a considerable number of papers dealing statistically with lung cancer and intrathoracic new growths have been published. In the majority, the conclusion has been reached that the incidence of lung cancer is on the increase, and that this increase is not merely apparent but real. In this communication it is not intended to review this literature but rather to approach the problem from an entirely fresh angle.[2]

When Dr. Bonser (1) from this Department published her paper in 1929 she reviewed twenty-two papers which had then recently been published, either on the Continent, in the United States, or in this country. In seventeen of these a claim was put forward that lung cancer was on the increase, while in only five was no such claim made. However, in her paper, which primarily dealt with Leeds, all the evidence was in favour of there being no increase in intrathoracic neoplasms in Leeds. In view of the fact that of all cases dying in the General Infirmary at Leeds 90 per cent. come to the post-mortem room, and the fact that the total number of autopsies may amount to as many as 800 in a single year, it seemed that such a finding was worthy of further investigation, as it is evident from the completeness of these figures that the post-mortem examinations at Leeds are unselected. Moreover, as the numbers dealt with in her paper are very large, they are therefore less likely to conceal an error.

Nature of Material Examined

From the published papers which deal with intrathoracic cancer it would appear that the sole source of the material analysed is the post-mortem room. No attention appears to have been paid to the steadily increasing

---

[1] Received February 28, 1935.

[2] Good bibliographies bearing on the statistics of lung cancer are given by Ask-Upmark, E., 1932, *Acta. Path. et Microbiol. Scand.*, ix. 159; Peters, W., 1932, *Z. Krebsforsch.*, xxxvii. 587; and Bonser, G. M., 1934, *J. of Hygiene*, xxxix. No. 2, 218.

number of patients who are admitted to the hospitals. In nearly every paper that we have seen the writer on this subject has confined his or her attention solely to a study of the proportion of intrathoracic cancers in total autopsies. While at the same time many have in addition considered the proportion of lung cancers found at autopsy to the total post-mortem cancers in all sites, no serious attempt has been made to examine the relation of the post-mortem lung cancers to the new patients admitted to the wards of the hospitals.

It is not unreasonable to expect that, if there be a large increase in the number of in-patients, there will also be a corresponding proportional increase in the number of cases of lung cancer admitted to the wards for treatment, other things being equal. Further, it is to be expected that this, in turn, would be reflected in an increase in the number of lung cancers appearing in the post-mortem room. The present inquiry, therefore, embraces the problem from this point of view. In dealing with the nation's death rate from various causes the Registrar-General records the number of deaths from each cause in every million of the living population of the country as a whole. In similar manner we have taken the number of cases of intrathoracic tumours, as proved at autopsy, and have calculated their proportion to the living population in the wards of the hospitals. In our case, however, we have calculated the number of intrathoracic cancers appearing in the post-mortem room for each hundred new patients admitted to the wards, and are presenting our results in percentages.

For the purpose of our inquiry we have analysed the figures of the teaching hospitals of London, the Provinces, and Scotland. These figures were obtained as part of a larger inquiry into the incidence of cancer in general in these hospitals, which it is intended to publish at a later date. The figures on which this paper is based were collected under the direction of the heads of the Departments of Pathology in the respective hospitals, who in each case appointed a member of his staff to go through the post-mortem records.[3] It was not considered advisable to make use of figures from the Middlesex Hospital, London, as it was felt that the provision of wards specially set aside only for cancer cases placed this hospital in a special position compared with other teaching hospitals, in that the autopsy figures might be unduly loaded with cancer cases, while, for similar reasons, the admission figures would not be representative of the teaching hospitals in general.

In view of the recent change in the outlook as to the histopathology of lung tumours, and the impracticability of reviewing past cases of intrathoracic tumours in the light of our present knowledge and ideas, the cases recorded as intrathoracic neoplasms depend, in the main, for their diagnosis on the morbid anatomical appearances *post mortem*, though in many cases confirmatory microscopical examination had been performed. Again, for

---

[3] The names of the individuals are shown in the list of acknowledgments at the end of this article.

the same reason, no attempt has been made to group the cases into carcinomata and sarcomata. Cases of oesophageal tumours and cases of Hodgkin's disease are not included in these figures. Excepting these two groups, all forms of primary malignant intrathoracic neoplasms are included in our figures. Throughout this communication the terms 'intrathoracic neoplasm' and 'cancer of the lung' are in general interchangeable.

Factors Capable of Influencing the Material under Investigation

Before discussing results, it might be advantageous to consider some of the factors which might influence the admittance of lung cancers to the wards of the teaching hospitals and which would subsequently determine their appearance at autopsy. The total number of intrathoracic cancers found at autopsy each year being few, these points will be dealt with at some length because any factor which may occasion the appearance of one or two extra cases each year may be sufficient to affect the figures of a hospital appreciably.

Cases of cancer of the lung which are admitted to the wards can be divided roughly into two large groups. In the first are the cases which are admitted under some other diagnosis than that of cancer of the lung. Once admitted, there the case may remain until the end, because the progress of the disease may render removal of the patient impossible. On the other hand, if, after admission, the case be definitely diagnosed as one of malignant disease of the lung, the patient, in the majority of cases, will, provided his condition permits, either be advised to go home, or be sent to a Poor Law Hospital. A case definitely diagnosed at out-patients as cancer of the lung would not, in the usual course of events, be admitted into a general hospital, except for reasons which place such a case in the next group, as, speaking in general, cases of cancer in any site which are unlikely to benefit from treatment in hospital are not admitted to the wards if they are fit to have treatment at home or are able to go on to another institution organized to take care of chronic and incurable conditions. Probably this first group has, in part, accounted for a great majority of the cases of lung cancer in the wards of the teaching hospitals, and still accounts for a considerable proportion.

In the second group are the cases which are admitted—in fact it could almost be said are deliberately selected for admission—because they clearly are, or probably will turn out to be, cases of lung cancer. In general, their admission is for the purpose of teaching, research in diagnosis, and, more recently, for ameliorative treatment or therapeutic research, more especially by X-ray and radium. For obvious reasons this group has been growing steadily of recent years and will possibly continue to increase in numbers for some time yet to come. It is almost certain that it is growing at the expense of the first group and possibly, in some hospitals, in addition to it. It is this group which can most seriously disturb the statistics of the disease,

and it is quite easy to understand how this can come about. This group is intentionally selected and collected. Its size will be determined largely by the outlook, interest, and zeal of those in charge of the wards of the teaching hospitals.

There are several factors which decide the appearance, after death, of any particular condition *post mortem*. In those hospitals where every death, where possible, is followed automatically by an autopsy, the factors are very largely those which determine the admission of the case to the ward of the hospital. In those hospitals, however, where only a certain number of those dying are examined in the post-mortem room, the post-mortem figures are, in the first place, dependent upon the admissions to hospital and, subsequently, upon a further selection after death : a selection which may be in part fortuitous and in part deliberate. Deliberate selection for the post-mortem room may operate in two ways : there may be selection of certain cases on account of the interest of the diseases from which they may have been suffering, or, conversely, selection may operate to the exclusion of certain cases because the diseases from which they have suffered are themselves not considered interesting. In the case of a hospital where only 25 per cent. of all patients dying reach the post-mortem room a misleading result can be obtained by a consideration only of the post-mortem figures. In such a hospital, if every case dying of lung cancer, or suspected lung cancer, be deliberately chosen for autopsy, it is theoretically possible for the *percentage of lung cancers in post-mortem examinations* to be four times as high as in a hospital where 100 per cent. of all cases dying come automatically to the post-mortem room.

Again, take the hypothetical case of a hospital where only 25 per cent. of patients dying are examined in the post-mortem room, and where the actual lung cancer incidence in the in-patients has not varied throughout the period under consideration. In the earlier days, when lung cancer excited but little clinical interest and its diagnosis in life was less satisfactory, only a certain fortuitous proportion of cases of those dying of lung cancer (possibly about 25 per cent.) would appear in the post-mortem room, while many would escape examination altogether, having been unrecognized as lung cancers in life. When, in more recent years, interest in this condition has become intensified and clinical diagnosis more certain, selection will have ensured a larger proportion of cases being examined after death. Looking at the autopsy figures of such a hospital an impression would be gained of a marked increase in the incidence of lung cancer in the later period. In the case of those hospitals with a consistently high percentage of post-mortem examinations after death, the lung cancer percentage would remain approximately the same throughout the whole period : because in the earlier period lack of skill in diagnosis during life and lack of interest in the condition would not prevent the cases reaching the post-mortem room, while on the other hand in the later period no amount of enthusiasm or skill in diagnosis would increase the number of cases coming to autopsy,

as in both periods practically all the cases dying have automatically come up for examination.

From what has been said it is evident that, to be of value, hospital statistics dealing with death from any particular condition should take into consideration the numbers of admissions to the wards, the numbers of all those dying in the wards, and the percentage of those dying which are subjected to autopsy.

In what follows it is not proposed to assess the part played by these possible and varying influences. They are put forward for consideration, and it will be seen from the figures of many of the hospitals that there are many opportunities for such factors to come into play.

TABLE I

Total Dying in Hospital and Percentages Examined in the Post-mortem Room

Centre.		1894–8	1899–1903	1904–8	1909–13	1914–18	1919–23	1924–8
Aberdeen	a	722	989	1,034	1,179	1,144	1,506	1,645
	b	28·2	17·7	20·3	21·3	13·7	19·9	48·6
Edinburgh Royal	a	3,321	3,787	4,108	4,191	4,277	4,670	5,328
	b	54·1	39·3	53·0	56·6	40·4	43·5	49·1
Glasgow West	a	1,788	2,246	2,493	3,106	3,219	3,077	3,183
	b	46·3	34·4	39·3	31·5	19·0	33·0	35·2
Glasgow Royal	a	3,043	3,664	4,289	4,497	5,283	4,911	5,378
	b	41·2	46·8	45·5	39·6	33·1	35·5	39·4
Guy's	a	2,875	3,327	3,705	3,762	3,540	2,965	2,831
	b	79·9	70·2	80·8	88·5	86·0	89·3	93·2
Leeds	a	1,146†	1,764‡	2,465	2,761	2,929	3,330	4,212
	b	81·8	81·3	88·7	88·4	80·9	86·0	89·4
London	a	—	—	1,423§	6,650	6,085	5,262	3,947
	b	—	—	90·3	84·5	55·1	60·5	74·5
Liverpool	a	1,243	1,477	1,645	1,379	1,325	1,436	1,596
	b	45·3	53·0	44·9	49·3	30·3	31·6	30·3
Manchester	a	2,092	2,184	2,390	3,233	3,752	4,134	4,073
	b	56·2	47·4	42·9	36·8	21·9	30·9	31·1
St. Bartholomew's	a	3,158	3,203	3,418	3,294	2,875	3,053	2,839
	b	82·7	79·8	80·3	80·9	70·2	65·2	65·5
St. George's	a	1,950	1,910	1,882	1,772	1,628	1,542	1,494
	b	78·3	77·3	77·5	87·2	68·6	67·6	73·2
St. Mary's	a	1,671	1,770	1,859	1,786	1,295	1,270	1,374
	b	58·8	63·7	66·5	62·2	55·5	73·1	84·0
St. Thomas's	a	2,806	2,964	3,271	3,321	2,771	2,371	2,315
	b	87·1	88·8	88·8	87·6	74·4	82·2	91·0
Sheffield	a	—	643	—	2,409	2,586	2,822	3,078
	b	—	44·6	—	25·4	10·5	26·0	37·1*
U.C.H.	a	—	816	1,514	1,511	1,317	1,622	1,705
	b	—	68.5	79·1	82·5	77·2	83·0	79·0
Total of deaths		25,815	30,744	34,073	46,234	43,926	43,971	44,998
Total of post-mortems		16,534	18,822	21,821	28,637	24,098	23,726	26,110
Percentage		64·4	61·2	64·0	61·0	54·8	53·9	58·0

　　a Deaths in hospital.
　　b Percentages of deaths examined in the post-mortem room.
　　* Number of deaths for 1926 and 1927 not available.
　　† Figures for 1897–8 missing.
　　‡ Figures for 1902 missing.
　　§ Figures for 1908 only.

Table I reveals the results of the varying practices adopted by the different hospitals with regard to the percentages of deaths which are followed by

autopsy. In general there is complete lack of uniformity, comparing the hospitals one with the other. In a few instances only, such as St. Thomas's, Leeds, and Guy's, is the percentage in each case more or less constant and maintained at a level sufficiently high as to suggest that autopsy is performed on every available case. Such a table as this must seriously impair faith in statistics confined entirely to the post-mortem room.

There may be yet another factor which can disturb the interpretation of such statistics. It is that in some hospitals a greater percentage of male than of female in-patients die in hospital.

TABLE II

Percentage of Admissions According to Sex Dying in Hospital

Period.		Glasgow Western.		Liverpool.		London Hospital.			St. Bartholomew's.*	
		M.	F.	M.	F.	M.	F.		M.	F.
1894–8	a	1,178	578	—	—	—	—	c	1,657	957
	b	9·54	7·00	—	—	—	—	d	8·85	6·74
1899–1903	a	1,542	704	92,900	54,800	—	—	c	1,614	943
	b	10·25	7·19	11·90	10·20	—	—	d	9·16	6·70
1904–8	a	1,669	924	100,000	64,500	838	589†	c	1,726	1,020
	b	9·02	6·88	11·70	10·77	11·11	9·06	d	9·16	6·89
1909–13	a	1,983	1,223	87,600	52,300	3,770	2,880	c	1,650	1,015
	b	8·19	6·68	8·51	8·37	9·12	8·01	d	8·63	6·60
1914–18	a	2,033	1,196	79,000	55,500	3,552	2,533	c	1,242	778
	b	7·84	6·66	8·45	9·33	7·31	6·83	d	8·43	5·84
1919–23	a	1,953	1,124	90,100	53,500	3,058	2,204	c	1,300	692
	b	7·61	5·69	9·33	8·07	6·59	4·83	d	6·59	3·49
1924–8	a	2,028	1,255	100,000	59,600	2,371	1,576	c	1,190	661
	b	9·02	5·50	7·54	6·46	5·71	3·83	d	5·38	2·92

* Percentages according to sex of admissions reaching the post-mortem room, the figure for deaths according to sex being unobtainable.
† 1908 only.
a Deaths.
b Percentage incidence of deaths in admissions according to sex.
c Autopsies.
d Percentage incidence of autopsies in admissions according to sex.

That this factor may exist is clear from Table II, which sets out according to sex the percentages of in-patients who die in the only four hospitals for which such figures are obtainable. It appears, too, that this sex discrepancy is tending to widen in each of the four hospitals.

Factors Influencing Diagnosis

Increased accuracy in diagnosis of lung cancer has undoubtedly taken place in recent years. In this country there have been two main sets of factors at work: one, improvements in methods of precision and in instrumental aids to diagnosis, and the other legislative. There is no necessity to enlarge on the undoubted—in fact overwhelming—importance of the first group. This is recognized on all hands as having had a world-wide influence. Hruby and Sweeney (2) consider that 'over 75 per cent. of the

diagnoses of cancer of the lung to-day are, or should be, correct'. Citing other authors, they state that a decade ago not more than 35 per cent. were correctly diagnosed. They quote Ferenczy and Matolosy as reporting 5 per cent. correct diagnoses from 1896–1900, 28·4 per cent. from 1917–25, and 50 per cent. in 1925, while, quoting Lubarsch's series, the correct diagnoses are given as 52 per cent. in 1920.

It is a little surprising, however, that in none of the communications on the subject of lung cancer has any notice been taken of recent legislation which must at least have played a big part in raising the standard of diagnosis of intrathoracic conditions in general throughout this country in the last twenty years.   In the first place, there is the legislation [4] which has regulated the establishment of tuberculosis medical officers, tuberculosis dispensaries, and sanatoria throughout the country, and under which compulsory notification of tuberculosis was established.   It requires no imagination to realize how profoundly such legislation must have gradually influenced for good the diagnosis of the whole group of respiratory tract diseases.   The effect of this legislation has, by the nature of things, required time for its full development, and in all probability was not felt until the post-war years. The reflected influence on the general practitioner was certainly not likely to have been instantaneous.   Thus to-day the average citizen of this country suffering from an obscure respiratory disease is subjected to a far more searching scrutiny than he would have received twenty years ago.   This has undoubtedly led to a better segregation of all the more chronic respiratory diseases into their various and proper categories.

But the potential influence which this legislation may have on the general level of the diagnosis of thoracic disease, and consequently on hospital statistics, does not altogether end there.   In many instances it appears that the tuberculosis officer sends the cases of lung cancer, which appear in the course of his clinical work, directly to the out-patient department of the teaching hospital of his area with a view to admission, though in point of fact such cases are frequently not admitted if the diagnosis is certain. This, we understand, is the case in Leeds—in fact, so much so that the Clinical Tuberculosis Officer, Dr. N. Tattersall, tells us that he does not now send many cases to the General Infirmary as frequently they are not admitted.   Thus, although in the case of Leeds this practice has not resulted in the admission of many cases specially sent up to out-patients by the local tuberculosis officer, it is obviously a potential source of cases of lung cancer, and may easily affect the statistics of any particular hospital which is prepared to admit them.

Again, in the Metropolitan area, tuberculosis officers of certain of the boroughs actually have their dispensaries established within the walls of the large teaching hospitals serving their areas.   This applies in the case of Guy's, St. Bartholomew's, St. Mary's, St. Thomas's, and University College Hospitals.   The possible influence of this innovation will be discussed later.

[4] Public Health (Tuberculosis) Regulation, 1912, issued December 19, 1912.

Under the Workmen's Compensation (Silicosis) Acts, 1918 and 1924, special provision for the medical examination of workers in the refractories industries was instituted, with the setting up in 1925 of a special medical board to examine periodically all workers engaged in these industries. The Act was extended in 1929 to cover the sandstone industry, and in 1930 the asbestos industry. It is, of course, not claimed that enough time has yet elapsed for this industrial legislation to have had much, if any, influence on the figures covered by the period of this inquiry. It is possible, however, that in the future it may have some effect on the statistics of lung cancer. In practice at least it means that a very considerable body of industrial workers in this country is now being subjected to a careful periodic scrutiny of their respiratory system.

TABLE III

Percentage Incidence in Admissions of Post-mortem Intrathoracic Tumours in Five-year periods from 1894 to 1928 Inclusive

Hospital.		1894–8	1899–1903	1904–8	1909–13	1914–18	1919–23	1924–8
Edinburgh	a	46,053	46,044	52,382	58,480	58,720	64,618	82,551
Royal	b	24	13	24	23	27	31	31
	c	0·052	0·028	0·045	0·039	0·046	0·047	0·037
Glasgow	a	29,989	33,663	39,729	42,626	52,307	53,246	73,570
Royal	b	20	13	17	20	28	21	28
	c	0·066	0·038	0·042	0·046	0·053	0·039	0·038
Glasgow	a	20,586	24,823	31,917	42,484	43,857	45,362	50,289
Western	b	14	8	13	13	9	11	30
	c	0·068	0·032	0·040	0·030	0·020	0·024	0·059
Leeds	a	17,276*	24,716†	32,269	38,119	47,358	47,931	63,086
	b	10	14	20	32	30	31	43
	c	0·057	0·056	0·060	0·083	0·063	0·064	0·068
Liverpool	a	8,304	15,371	17,888	19,570	21,112	22,044	28,261
	b	6	15	18	16	10	18	17
	c	0·072	0·097	0·100	0·081	0·047	0·081	0·060
Manchester	a	21,173	22,296	24,003	38,887	47,332	43,204	54,408
	b	17	24	11	33	23	30	43
	c	0·080	0·107	0·045	0·083	0·048	0·069	0·079
St. Thomas's	a	29,411	31,087	33,407	40,505	47,464	43,852	53,700
(London)	b	14	14	18	34	14	19	6
	c	0·047	0·045	0·053	0·083	0·029	0·043	0·011

a Admission to hospital.
b Intrathoracic new growths at autopsy.
c Percentage of intrathoracic neoplasms in admissions to hospital.
* Figures for 1897 and 1898 missing.
† Figures for 1902 missing.

Statistical Results

In Tables III, IV, and V are set out the numbers of admissions to hospital, the numbers of intrathoracic new growths occurring at autopsy, and the percentage incidence of post-mortem intrathoracic neoplasms in admissions to hospital, each grouped in five-year periods.

The above table deals with a group of seven hospitals in which it is quite clear at a glance that there has been no rise in the percentage incidence of

post-mortem lung cancers in their living populations. Before the War, in the figures for each of these seven hospitals there can be found occurring five-year periods showing a higher percentage incidence than actually ever occurred in the post-war period of the same hospitals. If the incidence, as shown, calls for any comment at all, it might be to the effect that in some hospitals there is possibly a reduction in the percentage incidence, but it is not desirable to stress this point, as the big variations in some of the individual figures suggest that the samples in each case are subject to many varying influences. Attention, however, should be drawn to the figures for Manchester, which should be compared with Duguid's own figures (3). By the above method of analysis there is no suspicion of any increase in the incidence of lung cancer. In 1894–8 the percentage incidence in admissions of intrathoracic neoplasms was 0·080 while in 1924–8 it was 0·079, or, expressed more simply, in the earlier period for every 10,000 admissions eighty cases of intrathoracic tumours appeared at autopsy. In the period 1924–8 a similar incidence is found. Whereas in Duguid's table the percentage of lung cancers in autopsies in 1891–5 was 1·28, in 1901–5 it had risen to 2·40, and in 1921–5 to 2·57. The percentage of autopsies to deaths has, however, been very low at Manchester throughout the whole period investigated, and, moreover, it has fallen persistently from 56·2 in 1894–8 to 31·1 in 1924–8. Thus out of 2,092 deaths in the first five-year period there are 1,176 autopsies, while in the last period there are only 1,299 autopsies out of 4,073 deaths. Here is plenty of opportunity for selection to play its part.

As it was possible to obtain access to the records of Guy's and St. George's Hospitals extending back for some years beyond the average period of our inquiry, the figures for these two hospitals are displayed separately.

Again, in these two hospitals, there is no satisfying evidence of any recent marked increase in lung cancer. In the case of Guy's, in the quinquennium 1883–7, the percentage figure is as high as 0·069 compared with 0·080 for the last five years of this inquiry, whereas in the case of St. George's Hospital in the period 1863–7 we find the figure is 0·067 compared with 0·077 for the five-year period sixty years later. Again, in 1888–92 the comparable figure of 0·063 was obtained. In view of the wide variability of the figures of both these two hospitals it is very doubtful if such slight increase as is shown in those of the terminal quinquennium can be regarded as indicative of any real increase in the rate of incidence of lung cancer in these hospitals, especially if the improved conditions of diagnosis be taken into account. At the same time, these figures refute the statement occasionally made that until recently cancer of the lung was a rare condition in this country.

Thus, in eight of these nine hospitals, this method of inquiry yields no evidence of any recent increase in lung cancer, while in the case of one, Guy's, such rise as occurs in the figures is unconvincing; this is discussed later.

TABLE IV

Percentage Incidence in Admissions of Post-mortem Intrathoracic Tumours in Five-year Periods

Five-year periods.	Guy's Hospital.			St. George's Hospital.		
	Admissions.	Intrathoracic neoplasms at autopsy.	% of admissions.	Admissions.	Intrathoracic neoplasms at autopsy.	% of admissions.
1843–7	—	—	—	16,294	6	0·037
1848–52	—	—	—	16,323	2	0·012
1853–7	—	—	—	17,700	5	0·028
1858–62	—	—	—	17,853	5	0·028
1863–7	—	—	—	*15,014	10	0·067
1868–72	24,482	7	0·029	18,148	8	0·044
1873–7	25,729	11	0·043	16,915	7	0·041
1878–82	24,305	11	0·045	18,739	9	0·048
1883–7	24,666	17	0·069	19,002	9	0·047
1888–92	27,465	9	0.033	20,623	13	0·063
1894–8	32,480	11	0·033	20,466	11	0·053
1899–1903	38,922	23	0·059	21,394	12	0·056
1904–8	41,410	21	0·050	23,069	15	0·065
1909–13	44,750	21	0·046	23,976	18	0·075
1914–18	43,788	11	0·025	21,633	12	0·055
1919–23	44,201	24	0·054	23,104	15	0·064
1924–8	50,953	41	0·080	24,518	19	0·077

* 4 years only.

TABLE V

Percentage Incidence in Admissions of Post-mortem Intrathoracic Tumours in Five-year Periods from 1894 to 1928 Inclusive

Centre.		1894–8	1899–1903	1904–8	1909–13	1914–18	1919–23	1924–8
Aberdeen	a	10,200	12,171	13,843	14,581	14,739	17,523	22,568
	b	1	1	5	2	2	5	15
	c	0·009	0·008	0·036	0·013	0·013	0·028	0·066
Birmingham	a	28,254	37,197	38,402	43,166	25,150†	47,558	54,127
General and	b	14	16	28	31	23	54	65
Queen's	c	0·049	0·043	0·072	0·071	0·091	0·113	0·120
London	a	—	—	14,036‡	77,253	84,236	92,100	82,589
	b	—	—	10	39	28	52	72
	c	—	—	0·071	0·050	0·032	0·056	0·087
St. Bartholo-	a	32,287	31,870	35,280	39,102	36,280	41,525	45,393
mew's	b	26	17	23	18	13	21	44
	c	0·080	0·053	0·065	0·046	0·035	0·050	0·097
St. Mary's	a	18,580	18,730	20,544	21,648	16,954	19,456	19,660
	b	5	5	5	11	10	11	32
	c	0·026	0·026	0·024	0·050	0·059	0·056	0·162
University	a	—	7,528*	15,452	19,939	23,237	23,590	29,631
College	b	—	3	16	14	12	23	43
	c	—	0·039	0·103	0·069	0·051	0·097	0·145
Sheffield	a	—	8,395	—	32,107	41,666	42,532	51,606
	b	—	2	—	6	5	20	23
	c	—	0·023	—	0·018	0·012	0·047	0·044

a Admissions to hospital.
b Intrathoracic neoplasms at autopsy.
c Percentage of intrathoracic neoplasms in admissions to hospital.
* 1901–3 only.   † 1916–17 missing.   ‡ 1908 only.

In Table V, similar information is set out in the remaining seven centres. These results have been grouped in one table because, in contrast to those in Table III, they present the highest percentage figure in each case in the 1924–8 period, and, therefore, may be considered by some to offer sufficient evidence to say that in the case of these hospitals a real rise may have taken place in the incidence of lung cancer towards the end of the thirty-five year period under investigation.

The post-mortem and other figures for Aberdeen and Sheffield for the earlier periods are patently very incomplete and need not be taken very seriously. In Table I can be seen the percentage of those dying in hospital which are subsequently examined in the post-mortem room. In the case of these two hospitals very small numbers were examined, more especially in the earlier period. The highest incidence figure obtained in both cases is still below that of the average of the teaching hospitals in general. It is probable, therefore, that, with the increase in the percentage of post-mortems performed in the later period, a truer picture has been obtained: the rising incidence possibly has been merely indicative of a climb from an artificially depressed level to a more normal level, not necessarily of a real increase in the incidence of lung cancer.

Three of the five remaining hospitals, St. Bartholomew's, St. Mary's, and University College, present a special feature in their administration which it is suggested may well account for some of the rise in the later years. In each, as has already been mentioned, there has been established a tuberculosis dispensary serving the area in which each of these hospitals is situated. In the case of St. Bartholomew's, the City of London Tuberculosis Dispensary was instituted in 1914. In dealing with the lung-cancer cases diagnosed at the dispensary, Dr. F. H. Young, the Tuberculosis Officer, in a personal communication, writes, 'I do occasionally refer the cases to the medical side of the hospital, but far more frequently take them into one of my beds at Brompton'. It is, however, only fair to state that Dr. Young goes on to say 'I feel pretty confident that the establishment of the Dispensary has nothing to do with the apparent increase of intrathoracic carcinoma'.

The tuberculosis dispensary was instituted at St. Mary's Hospital in 1915. Dr. A. B. Porteous, in a written communication, says, 'All cases diagnosed as cancer of the lung in my department are referred to the medical or surgical side of the hospital'.

At University College Hospital the tuberculosis dispensary was instituted in 1913. In this instance, the Tuberculosis Officer, Dr. J. A. Struthers, writes that such cases as he has had have been referred to the medical side of the hospital. However, he makes it quite clear that these altogether have been very few in number.

We are not anxious to overstress the influence which the presence, intramurally, of a tuberculosis dispensary might have on the increases shown in these hospitals, because at St. Thomas's Hospital there also has been

established a tuberculosis dispensary.   But in the case of St. Bartholomew's, St. Mary's, and University College Hospitals there are the definite statements of the Tuberculosis Officers concerned that cases of lung cancer are referred to the medical or surgical side, whereas in the case of St. Thomas's Hospital, where there is no rise, Dr. G. T. Hebert, the Tuberculosis Officer, states that cases referred to the resident assistant physician for admission to the general wards are 'usually not accepted', although Dr. Hebert admits some cases from his out-patient department to his own ward 'for a week or two, to investigate and teach my class on'.   This wording suggests that these cases do not in many instances provide material for the post-mortem room.   Thus, in the group of three hospitals where we know definitely that cases are admitted, having been previously diagnosed in the tuberculosis dispensary, there is a definite rise in the incidence of lung cancer *post mortem* since the establishment of the dispensaries, and on the other hand, in the case of St. Thomas's Hospital, where we are told that such cases are not usually admitted, there is no such increase.

At Guy's Hospital, the Tuberculosis Out-patient Department was not established until 1920.   Dr. Geoffrey Marshall, the Tuberculosis Officer, writes that when lung cancer is diagnosed at Tuberculosis Out-patients 'we usually arrange for the patient to be admitted to a Medical ward'.   This may well explain such a rise as is shown in the figures for Guy's.

From the figures at our disposal the average total number of new patients (including contacts in the case of St. Thomas's) each year attending these five tuberculosis centres together is approximately 3,570.

Without pretending to be able to assess the exact importance of this special feature in these five hospitals, we feel that these facts should be presented with the other evidence, as it seems reasonable to infer that the presence of a tuberculosis dispensary inside the walls of a teaching hospital may have some influence on the number of cases of lung cancer admitted to the wards, provided cases of lung cancer so diagnosed are admitted.

The rising figures for the London Hospital and those for the Birmingham hospitals both call for comment and possible explanation.   In the case of the former, Professor H. M. Turnbull has told us that both admission to the wards and permission for necropsy are influenced by interest in particular diseases on the part of members of the Visiting Staff, and certain physicians were undoubtedly interested after the War in thoracic neoplasms.

In the case of Birmingham, Professor G. Haswell Wilson suggests that an explanation for the rise shown in the combined figures of the Queen's and General Hospitals may perhaps be found in the advent of Professor Shaw Dunn to the General Hospital in 1919 and the succession to the same Chair by himself in 1922.   A year later Professor Wilson was invited also to join the staff of the Queen's Hospital.   This resulted in an increase in the percentage of autopsies performed, as prior to this period he writes, 'there was no one to push for examinations in all deaths'.   As the figures for the total deaths for the Queen's Hospital are not available, it is not possible to bring

forward figures to support this.   There is, however, good indirect evidence in that the combined numbers of autopsies at the two hospitals increased very substantially from 1,259 in 1894–8 to 3,339 in 1924–8, an increase of 165 per cent., while at the same time the number of deaths at the General Hospital showed a much smaller increase for the corresponding periods, namely, 1,855 and 2,852 respectively, an increase of only 53 per cent.

Again, during the period of this inquiry, at both St. Mary's and St. Bartholomew's Hospitals a change in the practice of selecting cases for autopsy is indicated.   This is clear from Table I in that in the case of the former there has been a marked rise in the percentage of deaths which are followed by autopsy and in the case of the latter there has been a considerable fall.

TABLE VI

Combined Figures of the Hospitals in Tables III, IV, and V for the Years 1894 to 1928 Inclusive, Showing Percentage Incidence in Admissions, in Deaths, and in Autopsies

Five-year period.	Total admissions.	Total intrathoracic cancers at autopsy.	Percentage in admissions.
1894–8	315,059	173	0·055
1899–1903	374,207	180	0·048
1904–08	420,595	234	0·055
1909–13	597,193	331	0·055
1914–18	625,833	257	0·041
1919–23	671,846	386	0·057
1924–8	786,912	552	0·070

Taking the figures of all the hospitals together we arrive at the results shown in Table VI.   Examined column by column it will be observed from the second column that there has been a very large increase in the total of admissions to hospitals, namely, from 315,059 in the first five-year period to 786,912 in the last five-year period, and from the third column that the total numbers of intrathoracic cancer have increased from 173 in the first quinquennium to 552 in the last.   Taken by itself the increase in the total lung cancers is considerable, but column four shows that, when the incidence of these post-mortem lung cancers is calculated as a percentage of the cases admitted to the hospital, their increase has done little more than keep up with the increase in admissions to hospitals.   In fact the incidence percentage which was 0·055 in the beginning of the thirty-five-year period was still but 0·057 in the 1919–23 period, showing a rise of less than 4 per cent. Practically the whole of the rise which has taken place in the thirty-five years has occurred during the last five years of the inquiry.

It is extremely unlikely that the increase shown in the last five-year period indicates a real increase.   In the first place, practically the whole of it is accounted for by five only out of the sixteen centres.   Moreover, in the case of each of these five centres special features have been indicated which might well have had an influence on their statistics : at least it would not

be wise to exclude the possibility. Again, such rise as is shown is not gradual but occurs as a sudden jump in the last five-year period. While reasons have been advanced which offer some explanation for the sudden rise in these five centres, it is probable too that increased interest in the condition and an improved standard of diagnosis have at the same time augmented these influences.

Aetiology

It is agreed by most writers that cancer of the lung is more common in the male. This higher incidence in males is claimed by some to be of aetiological importance, and in consequence some writers have attempted to find in our modern mode of life factors which might bring about this difference in sex incidence. The two most recent prominent changes in our mode of living which have been selected in support of their claim are the great increase in smoking and the use of the motor-car. The first as an aetiological factor has received no support from work in the laboratory. If in reality this was the main determining cause of the so-called increase in lung cancer, how can the supporters of this theory explain the fact that cancer of the tongue, larynx, and pharynx have not increased in proportion to the increase which they claim to detect in the case of the lung, which, after all, is the last part of the respiratory tract to be exposed to its influence?

The case against the motor-car is supported by two schools, composed of those who think the pollution of the air of our narrow streets by exhaust fumes is the determining factor and those who blame the tarring of the roads. The former hypothesis has nothing whatever to support it. No one has yet shown that garage hands are specially prone to lung cancer. If tarring of the roads is a responsible factor there has never been demonstrated any susceptibility to lung cancer in taxi-drivers, tram, or motoromnibus drivers and conductors, or in those who drive commercial vehicles or act as chauffeurs. Is there any evidence of a higher incidence in the thousands of men who tend our roads, or in those members of the Police Force or the Automobile Association and the Royal Automobile Club, whose daily occupation is to stand on duty at points of traffic concentration and at cross roads where it is reasonable to expect that suspension of road dust in the air would be at its maximum?

Tarring of the roads did not become general in this country until the War period, whereas the rise in the lung-cancer incidence, which some profess to see in Duguid's table, shows itself as early as 1901–5 and is firmly established by 1911–15. The accompanying Table VII given by Bridge and Henry (4) in a communication dealing with industrial cancers shows that workers in the industries closely connected with tar and other allied carcinogenic compounds require an exposure under fairly intimate circum-

stances for very long periods before cancer, mostly of the cutaneous surfaces, first appears.

<div align="center">TABLE VII</div>

<div align="center">*Duration of Employment*</div>

Duration of employment.	Pitch and tar.				Paraffin.	Mineral oil.		Total.
	Patent fuel works.	Tar distilling works.	Gas works.	Other industries.	Shale oil works.	Cotton mule spinning.	Other industries.	
Under 10 years	9*	9*	1*	2*	—	—	—	21
10–15 ,,	25	19	5	6	5	9	7	76
16–20 ,,	28	9	5	8	5	17	2	74
21–30 ,,	50	25	11	10	11	54	17	178
31–40 ,,	19	17	20	5	5	107	16	189
41–50 ,,	2	4	5	4	—	104	8	127
51–60 ,,	1	1	—	—	—	55	4	61
Over 60 ,,	—	—	—	—	—	6	—	6
Not stated	29	19	8	9	2	9	3	79
Total	163	103	55	44	28	361	57	811

* No pathological reports on any of these cases were obtained and probably they are benign warts.

It is reasonable to expect that lung cancer, if induced by inhalation of tar-contaminated road dust, would require at least as long a latent period before making its appearances.   Campbell (5) has recently shown that the exposure of mice to an atmosphere highly contaminated with a sample of road dust, containing 2 per cent. of tar, is capable of inducing malignant tumours of the skin.   It is significant, however, that up to the time of the publication of his article he had completely failed to induce primary lung cancer, although the experiments had been in progress for more than a year, whereas the first skin tumour appeared in six months.   By analogy it seems reasonable to expect that the inhalation of tarry dust would take longer in producing tumours of the lung in men than such frequent application of tar to the skin as occurs in the tar and allied industries referred to in the Table.   Thus, if indeed there be anything in this hypothesis, it is certainly not reasonable to expect lung tumours in man, in any numbers, for some years yet to come.   In short, tarring of the road has not been in progress for a sufficient length of time to produce the changes in the incidence of lung cancer which many claim they can detect by their statistical methods, especially those who find this increase commencing in the pre-war or early post-war years.

Sex incidence.   Our figures support the results of other writers who find lung cancer more frequently in males.   This can be seen in Table VIII.

The sex discrepancy as shown in this table is, however, certainly exaggerated, because an analysis of the hospitals, where the figures were available, shows that there is a considerable excess of all male autopsies, which excess is growing in recent years.

Thus from Table IX it will be seen that for every 100 male autopsies there were only 55 female in the last quinquennium, while immediately preceding the War for every 100 male there were 66 female. In our series there is over the whole period a total of 1,631 male lung-cancer cases and only 479 female, a preponderance of 3·4 males to each female. To arrive at a truer figure one correction should be made to allow for the ratio of male to female autopsies, and another (which is not accessible to us) to make allowance for the ratio of male to female admissions. As in the case both of admissions and of autopsies males predominate, it is probable that the above male to female ratio of 3·4 : 1 is too high and possibly should be nearer to 2 : 1.

TABLE VIII

Numbers of Intrathoracic Tumours According to Sex in Five-year Periods

Hospital.	1894–8 M.	F.	1899–1903 M.	F.	1904–08 M.	F.	1909–13 M.	F.	1914–18 M.	F.	1919–23 M.	F.	1924–8 M.	F.
Edinburgh	17	7	10	3	20	4	15	8	21	6	26	5	28	3
Glasgow Royal	16	4	10	3	12	5	15	5	19	9	13	8	22	6
Glasgow Western	8	6	5	2	9	4	9	4	6	3	6	5	19	11
Leeds	6	3	10	4	17	3	22	10	23	7	22	9	36	7
Liverpool	4	2	13	2	14	4	15	1	9	1	14	4	16	1
Manchester	14	3	21	3	8	3	27	6	22	1	26	4	33	10
St. Thomas's	12	2	11	3	13	5	24	10	11	3	14	5	5	1
	77	27	80	20	93	28	127	44	111	30	121	40	159	39
Aberdeen	—	1	—	1	4	1	2	1	1	1	4	1	13	2
Birmingham	11	3	12	4	25	3	24	7	21	2	41	13	57	8
London	—	—	—	—	7	3	29	10	23	5	41	11	63	9
St. Bartholomew's	20	6	9	8	19	4	12	6	11	2	13	8	36	8
St. Mary's	3	2	4	1	5	—	8	3	8	2	8	4	25	7
U.C.H.	—	—	—	—	13	3	10	4	11	1	14	9	31	12
Sheffield	—	—	2	—	—	—	4	2	4	1	18	1	16	7
St. George's	7	4	8	4	10	5	13	5	9	3	11	4	15	4
Guy's	10	1	17	6	10	11	15	6	8	3	18	6	39	2
	51	17	52	24	93	30	117	44	96	20	168	57	295	59
Total	128	44	132	44	186	58	244	88	207	50	289	97	454	98

That there are marked sex differences in other sites is shown in Table X, which contains the figures for the only hospitals which were able to supply the figures for admissions to hospital separated into the two sexes. From these figures it will be seen that, in these hospitals at any rate, cancer of the pancreas has a sex distribution not unlike that of lung cancer, while in the male malignant disease of the oesophagus is more than seven times more common than in the female, while gastric cancer has a twofold higher incidence in men than in women.

It is generally agreed that the total incidence of cancer of all sites is approximately the same in both sexes : in the ten-year period 1921–30 the Registrar-General gives the figures of deaths from cancer (all sites) per million living as 1,004 males and 986 females (6). As, however, malignant disease of the reproductive system (uterus and breast, ovary and fallopian tube) accounts for approximately 38 per cent. of all cancer in the female

TABLE IX

Post-mortem Examinations in Sexes, in Five-year Periods

Period.		Aberdeen.		Birmingham.		Glasgow Western.		Guy's.		Liverpool.		London.		St. Bart's.		St. Mary's.		Totals.	
		M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.
1894–8	a	135	69	838	441	1,178	578	1,449	859	368	196	—	—	1,657	957	608	369	5,055	2,891
	b	51 %		52 %		49 %		59 %		53 %		—		57 %		60 %		57 %	
1899–1903	a	107	67	1,083	632	1,542	704	1,419	919	508	275	—	—	1,614	943	676	451	5,407	3,287
	b	62 %		67 %		45 %		64 %		54 %		—		58 %		66 %		60 %	
1904–08	a	138	71	1,703	956	1,669	924	1,749	1,246	492	248	750*	535*	1,726	1,020	805	430	6,613	3,971
	b	51 %		56 %		55 %		71 %		50 %		71 %		59 %		53 %		60 %	
1909–13	a	165	87	1,367	931	1,983	1,223	2,028	1,320	390	291	3,213	2,331	1,650	1,015	721	391	9,534	6,366
	b	52 %		68 %		61 %		65 %		74 %		75 %		61 %		54 %		66 %	
1914–18	a	105	51	1,332	862	2,033	1,196	1,835	1,211	220	182	2,100	1,252	1,242	778	495	224	7,329	4,560
	b	48 %		64 %		58 %		65 %		82 %		59 %		62 %		45 %		62 %	
1919–23	a	210	99	1,642	898	1,953	1,124	1,681	967	303	152	1,921	1,264	1,300	692	615	313	7,672	4,385
	b	47 %		54 %		57 %		57 %		50 %		65 %		53 %		50 %		57 %	
1924–8	a	515	295	2,230	1,109	2,028	1,255	1,683	959	301	183	1,847	1,094	1,190	661	742	413	8,508	4,713
	b	57 %		49 %		61 %		56 %		60 %		59 %		55 %		55 %		55 %	

a Total post-mortems, male and female
b Percentage proportion of females to males.
* 1908 only.

and, of all malignant disease in the male, only approximately 6 per cent. is accounted for by cancer of the prostate, penis, testis, scrotum, and breast, a higher incidence in some other sites in the male is to be expected if the total cancer incidence in each of the two sexes is to be the same.

TABLE X

Combined Percentage Incidence of Post-mortem Cancers of Various Sites in Admissions* According to Sex for the Period 1894–1928, in Glasgow Western, Liverpool, London,† and St. Bartholomew's Hospitals

Site.	Cases.		Percentage in admissions.	
	Male.	Female.	Male.	Female.
Lung	413	130	0·0787	0·0300
Rectum	206	122	0·0392	0·0282
Colon and Caecum	424	319	0·0808	0·0737
Oesophagus	415	48	0·0791	0·0110
Pancreas	146	58	0·0278	0·0134
Stomach	812	347	0·1548	0·0802

* Males 524,248; Females 432,383.
† 1908–28 only.

It is no more remarkable that the incidence of pulmonary cancer is higher in men than women than that cancer of the pancreas, stomach, oesophagus, and other sites also shows a higher male incidence.

It is conceivable that an explanation of the varying site incidence in the two sexes will in the first place depend upon the attainment of a greater knowledge of the general factors concerned in the genesis of cancer rather than upon a search for possible localizing factors.

TABLE XI

Percentage Incidence of Post-mortem Lung Cancer in Admissions According to Sex

Five-year period.	Glasgow Western.		Liverpool.		London.		St. Bartholomew's.	
	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.
1894–8	0·065	0·065	—	—	—	—	0·106	0·035
1899–1903	0·033	0·020	0·153	0·037	—	—	0·051	0·056
1904–08	0·048	0·029	0·152	0·066	0·093*	0·046*	0·100	0·027
1909–13	0·038	0·022	0·135	0·032	0·070	0·028	0·057	0·035
1914–18	0·023	0·017	0·096	0·017	0·047	0·013	0·081	0·014
1919–23	0·023	0·025	0·124	0·060	0·088	0·024	0·055	0·045
1924–8	0·066	0·049	0·127	0·010	0·154	0·019	0·168	0·036

* 1908 only.

In a recent paper Bonser (7) draws attention to certain statistics which suggest that intrathoracic cancer is increasing at an unequal rate in the two sexes. Of the authors she quotes some few show this increased rate in women, though a majority find the increase is on the male side. In her own figures of Leeds, which are probably at least as complete as those of any of the authors she mentions, Bonser finds no such increase. In none of

the instances given do the authors present figures showing either (1) the proportion of each sex admitted to hospital, or (2) the proportion of total deaths followed by autopsy, or (3) the proportion of deaths for each sex which reached the post-mortem room.

Our own experience does not lend serious support to the suggestion that lung cancer in the male is increasing at a more rapid rate than in the female. It has only been possible to obtain the requisite figures for four hospitals, as the majority, while able to supply the total admissions to the wards, are unable to supply the admissions according to sex.

Table XI shows the figures we have been able to obtain. Those for Glasgow Western and Liverpool show no increase in either sex. In the case of St. Bartholomew's the extremes of variation in the five-yearly figures, especially of those for males, make it difficult to believe that any satisfactory conclusions can be safely drawn from them, there being an alternate rise and fall in each five-year period. Thus, comparing the 1894–8 figures for males with those of 1919–23, a 48 per cent. fall in the male incidence appears to have taken place, whereas a comparison between 1894–8 and 1924–8 shows a rise of 58 per cent. in the male incidence. The sampling is obviously very unsatisfactory. The case of the London Hospital, however, appears at first sight to support the suggestion that the incidence in men is rising more rapidly than in women. But in Tables I and II there is evidence to show that a marked change has been taking place during the period 1908–28 in the conditions at this hospital. Comparing the beginning with the end of this period, in the earlier years a higher percentage of cases dying went to the post-mortem room, a higher percentage of admissions died in hospital, while in the later years proportionately more deaths occurred among the male than among the female admissions. Again, Table IX shows that while there is a growing tendency to examine fewer cases (of both sexes) in the post-mortem room, this reduction is proportionately more marked in the case of the females.[5] In view of these changing conditions it is difficult to believe that any safe conclusions can be drawn from these figures of the London Hospital.

The figures quoted by Bonser from the Registrar-General's *Review* for 1930 are at first sight disturbing in showing not only a marked rise in the incidence of lung and mediastinal cancer in both sexes between 1911–20 and 1921–30, but also in that the male mortality from these conditions has increased proportionately very much more than the female.

But the Registrar-General himself, after noting that the male mortality was doubled, goes on to say, in the next sentence, that the rapidity of this increase 'suggests improved means of diagnosis'. Again, in the Registrar-General's *Review* for 1931 (8), a further increase in the rate for lung cancer is recorded. Now however it can be seen (Table XII) that, while the male rate is doubled, the female rate also is nearly doubled. The Registrar-

---

[5] The percentage in the case of male deaths followed by autopsy had fallen less than in the case of the females.

General's comments on the figures is 'The rate for cancer of the lung in males was twice as great in 1921–30 as in 1911–20, and was again doubled by 1931. This increase has been almost equally rapid at all ages over 35 in males, and the magnitude of the increase in both sexes suggests improved means of diagnosis as the cause '.

<div align="center">TABLE XII*</div>

Cancer Mortality Rates per Million Population (Standardized) in England and Wales for Certain Sites for Each Sex

Year.	All sites.		Lung.		Mediastinum.		Lung and mediastinum.	
	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.
1901–10	784	942	10·2	7·0	8·1	4·5	18·3	11·5
1911–20	897	959	12·7	7·0	9·2	4·6	21·9	11·6
1921–30	1,004	986	25·2	9·6	12·6	5·8	37·8	15·4
1926	1,011	995	23·3	9·2	13·3	6·0	36·6	15·2
1927	1,018	984	26·8	9·7	12·9	6·0	39·7	15·7
1928	1,032	1,000	32·0	10·4	13·3	5·4	45·3	15·8
1929	1,031	999	33·4	11·9	12·1	5·6	45·5	17·5
1930	1,031	987	40·2	13·9	13·1	5·3	53·3	19·2
1931	1,031	974	51·0	16·3	11·4	4·6	62·4	20·9

<div align="center">* Taken from the Registrar-General's Statistical Review 1931 (Text).</div>

It may well be, as indeed many believe, that with better diagnosis the more recent figures represent more accurately the actual incidence of cancer in the two sexes than did those of the earlier decades. In other words, the Registrar-General's figures for both male and female intrathoracic cancer may have been altogether too low in the case of both sexes in 1901–10, but with the error much more marked in the case of the male figures. The subsequent rise may merely represent a correction of this error. There is much in the figures to support such a supposition. In 1901–10 the Registrar-General's figures for male lung cancer was 10·2 per million compared with 7·0 per million females. This sex ratio does not agree with the experience in the post-mortem rooms of the teaching hospitals in this country, as is shown in Table VIII, where during the same period the figure for males is at least twice that for females, even after allowance has been made for the preponderance of males at autopsy.

Again, the figures of the Registrar-General (Table XIII) show that the total incidence of cancer (all sites) has itself undergone a similar, though less marked, swing in the same period, while similar increases and similar changes in sex incidence have taken place in the same period in internal sites other than the lung, notably the prostate, intestines, pancreas, kidneys and suprarenals, rectum and stomach. In fact, this table gives figures which show increases in the case of cancer of the prostate, pancreas, and intestines almost as dramatic as those for mediastinum and lung added together, while the standardized death-rate from cancer of the prostate has actually increased fourfold.

There is no special reason to suppose that the increases in any of these sites, as shown in the Registrar-General's figures, indicate a real increase in the incidence of cancer of these sites.   Nor is the observation necessarily of any greater significance because the increases are more marked in the males. Cancers of the external and accessible sites do not show corresponding increases or alterations in sex incidence, for which the explanation usually offered is that the most active factor affecting the Registrar-General's figures is likely to be that of improved accuracy of diagnosis, which it is to be expected would most affect the inaccessible sites.

TABLE XIII *

Cancer Mortality Rates per Million Population (Standardized) in England and Wales for Certain Sites for each Sex

Year.	Prostate.		Intestine.		Pancreas.		Stomach.	
	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.
1901–10	11·8	—	63·5	72·3	14·5	11·8	167·2	133·0
1911–20	26·5	—	96·8	109·2	16·7	13·1	186·4	139·0
1921–30	47·7	—	125·4	129·9	26·3	19·5	221·1	155·5
1926	47·9	—	131·5	135·4	26·0	21·2	222·2	163·2
1927	47·8	—	132·0	131·8	30·3	20·4	229·0	157·0
1928	53·8	—	132·5	138·5	28·8	21·0	227·4	161·5
1929	56·4	—	134·3	138·6	30·3	20·0	237·2	164·6
1930	54·9	—	136·9	138·4	29·4	23·8	233·7	162·8
1931	56·2	—	135·7	136·3	28·7	21·6	230·5	155·5

* Taken from the Registrar-General's *Statistical Review* 1931 (Text).

If a further reason be required to explain why the increase of cancer in the internal sites, as shown in the Registrar-General's *Review*, is more marked in males than females, might it not be worth while to consider this as, in part, a possible result of the Natural Health Insurance Acts?   Below (p. 342) is a table which shows the proportion of the two sexes which are entitled to benefit under the Acts.

Without wishing to labour the point, it appears reasonable to suggest that those entitled to free medical benefit will, in general, seek medical aid earlier and more often than those not so fortunately placed.   In the long run this should lead to a greater degree of accuracy of diagnosis in the case of the insured, as compared with the uninsured, not only in cases of internal cancer but in all internal disease.   The table shows that the number of males who are entitled to medical benefits is nearly double the figure for females.   It is tempting to ask if these increased opportunities (which operate in the case of two males for every one female and which are available to a very large proportion of the adult population of Great Britain) may not have assisted and accelerated the general improvement in the standard of diagnosis, and helped in correcting the inaccuracies of diagnosis in internal cancer (including intrathoracic cancer) which undoubtedly existed in the earlier decades.

It is now necessary to ask ourselves two questions : (1) What do we, who undertake these inquiries, really desire to know ? (2) Which of the three methods of analysis will bring us nearest the truth : is it more accurate to calculate the relation of post-mortem room intrathoracic neoplasms to admissions, to deaths, or to autopsies ?

With regard to the first question, there will be universal agreement in answering that the object of all such investigations is to find out if the incidence of cancer of the lung in the population at large is, or is not, on the increase.

TABLE XIV

Estimated Number of Persons in Great Britain Entitled to Medical Benefits Under the National Health Insurance Acts

Compiled from the Annual Reports of the Ministry of Health (England and Wales) and the Department of Health for Scotland.

	Men.	Women.	Total
1912	—	—	—
1913	—	—	—
1914*	9,667,400	4,019,800	13,687,200
1915†	9,947,400	4,146,600	14,094,000
1916	10,316,000	4,531,800	14,847,800
1917	10,514,300	4,853,000	15,367,300
1918	10,704,500	5,182,500	15,887,000
1919	10,308,300	5,138,500	15,446,800
1920	10,214,600	5,064,000	15,278,600
1921	10,244,900	4,904,600	15,149,500
1922	10,215,200	4,897,000	15,112,200
1923	10,262,800	4,912,000	15,174,800
1924	10,497,300	5,100,100	15,597,400
1925	10,641,300	5,193,400	15,834,700
1926	10,927,400	5,325,700	16,253,100
1927	11,077,900	5,419,600	16,497,500
1928	10,980,800	5,572,600	16,553,400
1929	11,133,700	5,650,100	16,783,800
1930	11,255,300	5,757,000	17,012,300
1931	11,436,000	5,795,700	17,231,700

* The 1914 figures cover January 12–December 31. The later figures relate to calendar years.
† The figures for the years 1915–19 involve certain approximations.

With regard to the second question, it is generally recognized that the hospital population is not a true sample of the general population, so that any result obtained will only reflect a distorted image of the real picture. But in answering it, we ourselves have no hesitation in saying that we consider we will come nearer to the truth if we employ as our basis of comparison the number of cases of intrathoracic neoplasm appearing in the post-mortem room for each hundred new cases admitted to hospital than if we use the numbers appearing for each hundred deaths in hospital or in each hundred autopsies, as do most writers on this subject. It is perfectly true that the admissions to hospital are a very much selected sample of the

population at large, but the deaths in hospital are a further selection of that sample, while the cases which are subjected to post-mortem examination are yet again selected, consciously and unconsciously, from those dying in hospital.   In other words, the cases subjected to autopsy reach the post-mortem room as a result of three processes of selection, whereas the admissions to hospital undergo one selection.   It is for this reason that here we are only seriously considering and discussing the results obtained in a study of the relation of post-mortem room intrathoracic cancer to admissions to hospital.

If the reader be prepared to accept this method of approach to the problem he will find it difficult to make out a serious case for any appreciable increase in the incidence of intrathoracic neoplasia in the period 1894–1928, more especially when he remembers that the increase in the figure for 1924–8 is almost entirely accounted for by the figures of five hospitals only out of the sixteen.

The clinician will say that, compared with the two decades preceding the War, he is satisfied that he is seeing more cases of intrathoracic neoplasm in his consulting-room, in the wards, and at the out-patient department of the large hospital.   That is not denied.   It is almost certain that he does. But that does not necessarily indicate that the condition is actually on the increase.

Summary

1. A new method of approach to the statistical problem of intrathoracic neoplasia is presented.

2. The evidence afforded by this method does not support the widely-held view that the incidence of intrathoracic neoplasia is appreciably on the increase, especially if due allowance be made for the altered conditions of to-day in comparison with those of the pre-War period.

3. Out of sixteen hospitals, eight (Edinburgh Royal, Glasgow Royal, Glasgow Western, Leeds, Liverpool, Manchester, St. George's, and St. Thomas's (London)) certainly show no increase, three (Aberdeen, Guy's, and Sheffield) present indeterminate results; while five only (Birmingham, London, St. Bartholomew's, St. Mary's, and University College) show a frank increase.

4. In each of these five hospitals showing an increase there are associated special circumstances which may well have contributed to the increase.

5. Clinical and experimental evidence does not favour the suggested aetiological factors brought forward by those who suppose a real increase.

6. Legislation in the present century may have introduced modifying factors when comparing statistical results of the post-War and pre-War periods.

post-mortem room records in their charge, and to those members of their
staffs who examined the records and provided the material on which this
paper is based, and to Dr. G. M. Bonser for the use of her material dealing
with the Leeds General Infirmary:

Hospital.	Director.	Investigator.
Aberdeen Royal Infirmary	Prof. T. E. Shennan	Dr. J. G. Thomson
Birmingham General and Queen's	Prof. Haslow Wilson	Dr. O. Brenner
Edinburgh Royal Infirmary	Prof. Lorrain Smith	Dr. T. R. R. Todd
Glasgow Royal Infirmary	Prof. J. H. Teacher	Dr. J. S. Faulds
Glasgow Western Infirmary	Prof. R. Muir	Dr. A. A. Charteris
Guy's Hospital, London	Prof. R. Donaldson	Dr. R. C. Brock
Leeds General Infirmary	Prof. M. J. Stewart	—
Liverpool Royal Infirmary	Prof. J. H. Dible	Dr. R. Y. Dawbarn
London Hospital, London	Prof. H. M. Turnbull	Dr. D. C. Carroll
Manchester Royal Infirmary	Prof. J. Shaw Dunn	Dr. W. Susman
St. Bartholomew's Hospital, London	Prof. E. H. Kettle	Dr. J. Maxwell
St. George's Hospital, London	Dr. J. E. Taylor	Dr. R. D. Marnham
St. Mary's Hospital, London	Dr. W. D. Newcomb	Dr. J. W. Orr
St. Thomas's Hospital, London	Prof. L. S. Dudgeon	Dr. D. P. Marks
Sheffield Royal Infirmary	Prof. J. S. C. Douglas	Dr. H. H. Gleave
University College Hospital	Prof. A. E. Boycott	Dr. W. G. Barnard

REFERENCES

1. Bonser, G. M., *Journ. of Hygiene*, Lond., 1929, xxviii. 340.
2. Hruby, A. J., and Sweeney, H. C., *Arch. of Int. Med.*, Chicago, 1933, lii. 497.
3. Duguid, J. B., *Lancet*, Lond., 1927, ii. 111.
4. Bridge, J. C., and Henry, S. A., *Report of International Conference on Cancer*, Bristol,
   1928, 258.
5. Campbell, J. Argyll, *Brit. Journ. Exper. Path.*, Lond., 1934, xv. 287.
6. Registrar-General, *Statistical Review*, Lond., 1930, New Annual Ser. No. x. 57.
7. Bonser, G. M., *Journ. of Hygiene*, Lond., 1934, xxxiv. 218.
8. Registrar-General, *Statistical Review*, Lond., 1931, New Annual Ser. xi. 64.

SUGAR TOLERANCE IN OBESE SUBJECTS
A REVIEW OF SIXTY-FIVE CASES [1]

By ROBERTSON F. OGILVIE

(From the Pathology Department, University of Edinburgh, and the
Dietetic Department, Royal Infirmary, Edinburgh.)

LABBÉ and Boulin (12), Allison (1), and John (8, 9), have carried out sugar tolerance tests on numbers of obese people, and found that while some possess a normal tolerance for sugar, others exhibit varying degrees of diminished tolerance, the ultimate expression of severe intolerance clinically being diabetes. This is in agreement with the well-recognized association between obesity and diabetes. In an analysis of 1,063 cases of diabetes Joslin (10), for example, states that obesity preceded the onset in 40 per cent., though Root and Miles (16) place the figure at a lower level, viz. 20 per cent. On the other hand, it is interesting to note that several cases are on record of obese subjects having attacks of symptoms such as might have been produced by an overdose of insulin, and during the occurrence of which an unmistakable hypoglycaemia was present. Such cases are reported by Harris (6), and Winans (18). Harris (7) also reports the case of an obese subject with a blood-sugar of 45 mg. per cent., but in whom there were no symptoms suggesting hypoglycaemia.

A consideration of these facts suggests that for a time, probably during the early years of the obese state, the islands of Langerhans are unduly active, and that thereafter they lose vigour, their secretion becoming normal in amount and finally deficient. Passage from a phase of hyperinsulinaemia and increased sugar tolerance to one of hypo-insulinaemia and decreased sugar tolerance is a phenomenon, which so far has never been proved to exist in relation to obesity, and it was primarily with a view to investigating the possibility of its occurrence that this research was undertaken. It will be understood from what has been said, that to prove the point attention had in particular to be given to those obese subjects who gave a short history of overweight. As the research proceeded other points of interest were investigated, viz. the relation of sugar tolerance to the duration of the obese state, to the percentage overweight, to age, and most important of all, to ovarian function. Finally, since Ogilvie (13) showed that in some obese subjects the islands of Langerhans are hypertrophied, the relation of this finding to the

---

[1] Received March 15, 1935.

No.	Sex	Age	Percentage overweight.	Duration of obesity in years.	Fasting.	Blood-sugar in mg. %. After 50 grm. glucose.				Glycosuria.		Menstruation.
						½ hr.	1 hr.	1½ hrs.	2 hrs.	Before test.	After test.	
1	F	35	106	17	130	171	155	148	130	—	—	Regular.
2	F	39	66	14	110	140	110	98	94	—	—	,,
3	F	29	82	4	93	121	150	128	114	—	—	,,
4	F	46	40	12	94	172	156	102	90	—	—	,,
5	F	35	40	13	111	195	180	150	134	—	—	,,
6	F	31	98	5	101	125	126	126	93	—	+	,,
7	F	49	40	4	95	125	127	118	114	—	!	Menopause occurring.
8	F	32	34	7	96	135	126	126	126	—	!	Regular.
9	F	32	49	2¼	94	132	125	109	96	—	—	,,
10	F	34	31	1	76	89	129	112	107	—	—	,,
11	F	26	82	4	75	120	82	91	77	—	—	,,
12	F	42	53	2	92	125	93	90	92	—	—	,,
13	F	29	31	*⅜	84	118	94	94	98	—	—	,,
14	F	60	25	18	114	186	159	96	70	—	—	Menopause at 45 years.
15	F	35	42	1	85	118	118	116	88	—	—	Regular.
16	F	35	30	6	111	153	98	82	101	—	—	,,
17	F	48	31	18	120	183	151	149	119	—	—	,,
18	F	30	44	9	89	167	170	150	127*	—	—	,,
19	F	66	67	43	100	199	136	100	93	—	—	Menopause at 45 years.
20	M	49	71	10	89	137	152	126	98	—	—	—
21	F	58	80	18	89	129	152	130	119	—	—	Menopause at 52 years.
22	F	24	57	4	107	150	119	116	116	—	—	Regular.
23	F	54	58	10	78	125	168	154	158	—	—	Menopause occurring.
24	F	48	31	9	104	146	126	107	99	—	—	Menopause at 37 years.
25	F	46	47	5	100	126	144	153	95	—	—	Menopause occurring.
26	F	47	37	20	129	203	180	160	124	—	—	Menopause at 45 years.
27	F	52	38	17	103	156	138	108	99	—	—	Menopause at 49 years.
28	F	23	34	4	83	138	120	87	—	—	—	Regular.
29	F	38	37	13	106	174	152	127	99	—	—	,,
30	F	24	40	1½	98	137	151	133	113	—	—	Before unilateral oophorectomy 7/28 : after, 3/28 and loss scanty.

No.	Sex											Remarks
31	F	41	32	8	107	170	143	120	110	–	–	Regular.
32	F	33	75	13	80	139	126	105	86	–	–	,,
33	F	58	57	25	114	190	95	100	100	–	–	Menopause at 47 years.
34	F	25	42	¾	126	175	220	155	119	–	–	1 spot—7–12 weeks.
35	F	48	38	12	102	160	160	131	115*	–	–	Menopause occurring.
36	F	44	46	2⅔	101	185	163	134	125	–	–	Sterilized by radium.
37	F	42	43	7	85	143	104	90	81	–	–	Regular.
38	F	43	22	5	110	155	141	119	110	–	+	Menopause occurring.
39	F	59	45	34	107	209	261	194	179	–	–	Menopause at 49 years.
40	F	34	30	⅜	87	164	162	130	87	+	–	Sterilized by deep X-rays.
41	F	49	63	25	137	157	210	190	170	–	–	Regular.
42	F	36	34	7	75	146	119	87	70	–	–	,,
43	F	29	67	2⅚	100	134	118	107	96	–	–	,,
44	F	34	28	9	118	175	141	123	111	–	–	,,
45	F	36	29	10	107	175	157	134	118	–	–	Amenorrhoea for 2 yrs. 10 mths. since birth of last child.
46	F	29	32	2⅚	120	189	155	135	115	–	–	Regular.
47	F	39	80	12	130	220	260	210	145	+	+	Menopause at 54 years.
48	F	57	14	27	170	250	295	350	280	+	+	Menopause at 47 years.
49	F	53	67	12	112	155	155	145	98*	+	–	Menopause at 50 years.
50	F	65	25	25	107	194	146	123	107	–	–	Regular.
51	F	28	44	4	93	153	126	109	93	–	–	,,
52	F	35	37	7	100	143	169	134	109	–	–	Menopause at 38 years.
53	F	60	17	4	89	150	106	86	80	–	–	Scanty: 1–2 days. / 2–12 months.
54	F	29	40	4	104	143	170	139	109	–	–	Menopause occurring.
55	F	45	85	19	91	163	164	139	119*	–	+	Menopause at 52 years.
56	F	60	74	38	111	199	239	234	168*	–	+	Regular.
57	F	34	33	3	92	117	92	94	94	–	–	,,
58	F	27	38	3¾	109	141	86	102	119	–	–	Regular.
59	M	36	32	8	99	163	105	72	79	–	–	,,
60	F	25	49	5	102	163	157	127	102	–	–	Regular.
61	F	50	137	28	103	121	187	155	128	–	–	Menopause occurring.
62	F	60	82	24	122	168	187	154	110	–	–	Menopause at 48 years.
63	F	54	36	17	115	165	176	140	125	–	–	Menopause at 37 years.
64	F	50	57	14½	110	190	139	112	110	–	–	Menopause at 47 years.
65	F	62	46	13	100	146	123	121	117	–	–	Menopause at 49 years.

* Since it has obviously been missed, the peak of each of these cases has been plotted in the graphs at a slightly higher level than the figures given.

tolerance of obese subjects for sugar also presented a problem for consideration.

Method of Investigation.

All the subjects with two exceptions were women. Each patient having fasted since 9 p.m. the previous evening reported at the Dietetic Out-patient Department at 8 a.m. and was put to rest in bed. At 9 a.m. $\frac{1}{2}$ c.c. of blood was taken by venepuncture at the elbow, and of this 0·2 c.c. was used for estimation of the blood-sugar. At the same time the patient was asked to empty the bladder and a sample of urine was tested for sugar and acetone. Thereupon she was given 50 grm. of glucose in a tumblerful of water flavoured with lemon juice. Further samples of blood were taken at half-hour intervals up to two hours, at the end of which time a second specimen of urine was obtained and tested for sugar and acetone. The blood-sugar was estimated by the method of Hagedorn and Jensen (4).

The patient's history was carefully investigated. Points given special attention were the occurrence of parental and familial obesity, date of onset and duration of the obese state, the relation of the onset to any particular event in the patient's life, the existence of any menstrual abnormality, the date of her menopause, and the composition of her daily diet. Height and weight were taken, and the percentage overweight was then calculated with the help of tables [2] of standardized weights.
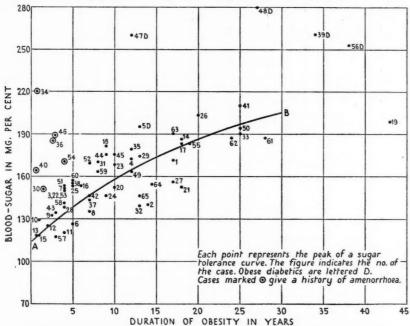
Results of Investigation

The facts accruing from an examination of 65 obese subjects are briefly arranged in the table on p. 346 and can be analysed as follows:

1. *Relation of sugar tolerance to duration of obesity.* In Graph I all the cases have been plotted according to the duration of the obese condition in each instance. No account is here taken of age. The method adopted has been to chart each case as a single point representing the peak of the sugar-tolerance curve. In this way the confusion which would have been created by plotting a large series of individual curves has been avoided, and the conclusions to be drawn have in no way been obscured. Each case is numbered, and those who have become diabetic (5, 39, 47, 48, and 56) are marked with a D.

In interpreting this chart it would be advisable to omit two groups of cases, viz. the obese diabetics mentioned above, and also Cases 30, 34, 36, 40, 46, and 54, which have a sugar tolerance definitely below that of the other cases with a corresponding history of obesity, and all of which have in common a gynecological abnormality to be described later. Omitting these groups the

[2] Published by the Association of Life Insurance Directors and Actuarial Society of America, New York, 1912, p. 38.

average trend of the sugar tolerance may be taken to be represented by the line AB. This line shows that as the duration of the obese state increases a progressive diminution occurs in sugar tolerance. The curve also suggests that the tolerance falls more rapidly during the earlier years of the obese condition than the later years, though the paucity of cases with a history of more than twenty year's obesity makes this conclusion uncertain.
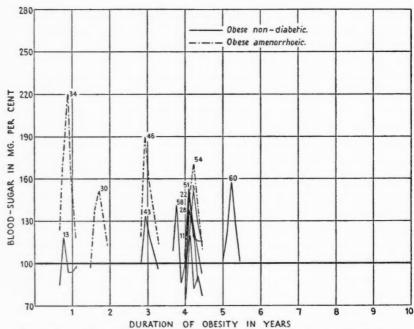

GRAPH I. Sugar tolerance in relation to duration of obesity (irrespective of age).

In Graph I, however, no account is taken of the influence of age on sugar tolerance. Tolerance for sugar, as is well known (17), and as will be demonstrated also in this series of cases, diminishes steadily throughout life. Consequently it is illogical to compare the sugar curve of a patient in the third decade with that of one in the sixth decade. To eliminate the influence of the age-factor as much as possible, the cases were grouped in decades and again charted according to the duration of the obesity. The charts in Graph II (a, b, c, d, e) were constructed after this manner.
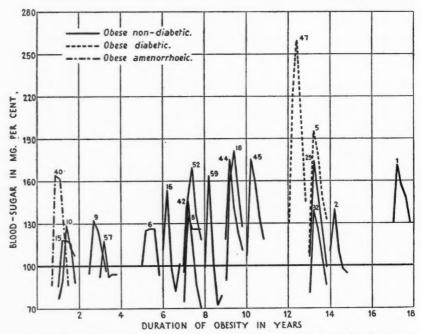
As in the case of Graph I it would be better to omit from Graph II Cases 30, 34, 46, and 54 in a, Case 40 in b, and Case 36 in c, since these form, as already mentioned, a distinctly separate group. The curves of obese subjects who have become diabetic are represented by evenly broken lines.

Before proceeding to an interpretation of the charts in Graph II, it is advisable to define the limits of the normal sugar curve in people between 20 and 70 years of age. According to investigators who have employed the Hagedorn-Jensen method, e.g. Kjer (11) the fasting blood-sugar is generally
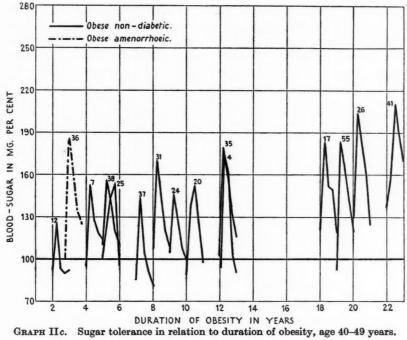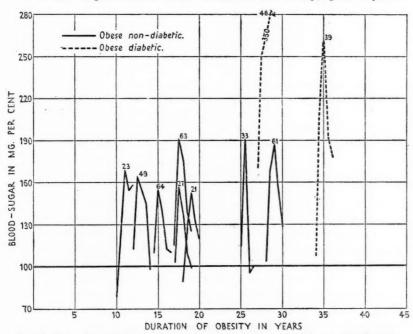
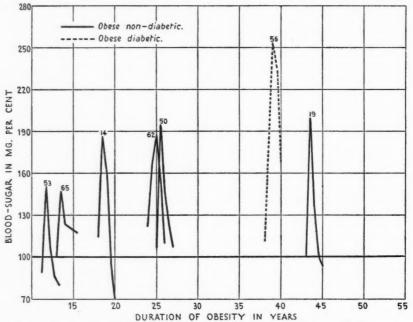GRAPH IIa. Sugar tolerance in relation to duration of obesity, age 20–29 years.

GRAPH IIb. Sugar tolerance in relation to duration of obesity, age 30–39 years.

GRAPH IIc. Sugar tolerance in relation to duration of obesity, age 40–49 years.

GRAPH IId. Sugar tolerance in relation to duration of obesity, age 50–59 years.

considered to lie between 80–100 mg. per cent. After 50 grm. of glucose the blood-sugar rises in about three-quarters of an hour to between 140-160 mg. per cent. Thereafter it falls and reaches normal in one and a half to two hours. As already mentioned, Spence has put forward evidence to show that

GRAPH II e. Sugar tolerance in relation to duration of obesity, age 60–69 years.

sugar tolerance decreases with advancing years, but a rise above 180 mg. per cent. is generally taken as representing an abnormally low sugar tolerance (Hansen 5, Petrén 14). Finally, although figures in support of the statement are scarce, most investigators would agree that a rise of less than 35 mg. per cent. above the original fasting level suggests an abnormally good sugar tolerance.

A consideration of Graph II a in which are plotted all cases in their third decade, shows that there is a steady fall in tolerance between case 13 with a history of eight months' obesity, and Case 60 with a history of five years. This progressive diminution in tolerance is also demonstrated by cases in the fourth, and particularly in the fifth decade where the history of obesity increases in duration to 17–22 years. Cases are less numerous in the sixth and seventh decades, but the arrangement of such cases as have been obtained at these age-periods favours the same conclusion. The charts of Graph II from which the influence of the age factor has been largely eliminated thus corroborate the relationship between degree of sugar tolerance and duration of obesity as was indicated by Graph I.

The individual curves may now be examined in more detail. In the third

decade (Graph II *a*) there are two curves, 13 and 43, each with a total rise of 34 mg. per cent.   In the fourth decade (Graph II *b*) Case 15 has a rise of 33 mg. per cent., Case 57 a rise of 25 mg. per cent., and Case 6 a rise of 24 mg. per cent.   In the fifth decade (Graph II *c*), Case 12 has a rise of 33 mg. per cent.   Each of these cases thus has a curve with a total rise of less than 35 mg. per cent., and as already mentioned it would be generally agreed that low curves of this type suggest increased sugar tolerance.   It will be noted, moreover, that the members of this group have one point in common, viz. a short history of obesity, the longest being 5 years in Case 6.   Case 2 in Graph II *b* at first sight falls into this group, for the initial rise is only 29 mg. per cent., yet it is exceptional in that the case has a history of fourteen years' obesity. The discrepancy, however, between the fasting level and the end-point of the curve makes it difficult to assess its true value, so that it is best omitted.

Excepting the above-mentioned, those cases with a history of obesity up to eleven years have curves which fall within limits indicating normal sugar tolerance.

Amongst the remainder, i.e. cases with a history of obesity over eleven years, some continue to fall within normal limits, while others show evidence of slightly diminished tolerance, e.g. Cases 17 and 55 (fifth decade) with curve-peaks of 183 mg. per cent., Case 61 (sixth decade) with a peak of 187 mg. per cent., and Cases 14 and 62 (seventh decade) with peaks of 186 and 187 mg. per cent. respectively. Others show evidence of definitely diminished tolerance, e.g. Cases 26 and 41 (fifth decade) with peaks of 203 mg. and 210 mg. per cent., and Cases 50 and 19 (seventh decade) with peaks of 194 mg. and 199 mg. per cent.

Finally, markedly diminished tolerance is seen in cases 5 and 47 (fourth decade), 39 and 48 (sixth decade), and 56 (seventh decade).   All show an abnormally great rise and a delayed fall, and the second specimen of urine in every case gave a positive Fehling's test for sugar.   These cases had thus passed into the phase of diabetes. It will be noted that the period of obesity preceding the onset of diabetes shows considerable variation—from twelve years in Case 47 to thirty-eight years in Case 56.
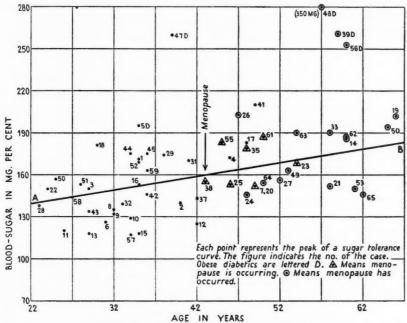
These curves suggest that during the first five years of the obese condition one-third of the subjects (6 of 18) have an increased tolerance for sugar, while the remainder have normal tolerance.   After this period the sugar tolerance of all obese subjects lies within normal limits up to a duration of eleven years' obesity.   Some exhibit normal tolerance even after eighteen years. During these years, nevertheless, tolerance for sugar steadily diminishes, so that after eleven years cases of lowered tolerance make their appearance, and after eighteen years every case without exception in this series exhibits a tolerance which is slightly or definitely below normal. Tolerance ultimately becomes so deficient that the subject passes into diabetes.   Among the cases under review diabetes supervened after periods of twelve to thirty-eight years' obesity.

Assuming that sugar tolerance is an index of the working capacity of the islands of Langerhans, it can be deduced that while in some obese people (probably about one third) there is a preliminary phase of hyperinsulinaemia followed by one of normal secretion, in the majority of cases the secretion of insulin is even in the earliest years normal. In both groups the phase of normal secretion ultimately gives way to one of deficient secretion.

The cause of this change in tolerance is difficult to explain. Is it possible for the factor effecting the change to be dietetic? In an analysis of 523 cases of obesity Dunlop and Murray Lyon (2) found that a few cases confessed to having grossly overeaten for many years. But a much commoner finding (45 per cent. of their cases) was a wrongly balanced diet with a preponderance of starchy foods. In some cases a high fat intake was noted, but this was not nearly so common a feature. The consumption of excessive quantities of carbohydrate naturally acts as a stimulus to the secretion of insulin, and since there is evidence to show that insulin is necessary for the utilization of fat, excess of the latter might have a like effect. But in this series evidence of hyperinsulinaemia has been observed in only six cases, all of which give a history of not more than five years' obesity. The remaining cases (12) in this period have a normal tolerance for sugar and, therefore, a normal secretion of insulin. Assuming a dietetic stimulus, it is difficult to explain the difference in response. The phase of hyperinsulinaemia, moreover, when it occurs, is not long maintained (apparently not more than five years). The continued dietetic demand leads in all cases to lessened capacity for secretion and ultimately to a state of more or less exhaustion. Consequently the sugar tolerance progresses through a normal phase to one of gross deficiency.

2. *Relation of sugar tolerance to percentage overweight.* To investigate the possibility of such a relationship the cases were grouped in decades, so that the influence of age was again largely eliminated, and plotted according to their percentage overweight. The charts have not been printed, but it can be stated that the average tolerance in each decade is indicated by a horizontal straight line. In other words, sugar tolerance in the obese subject is in no way related to the amount of overweight. Taking specific cases, it is seen, for example, that in the fourth decade Case 32 with 75 per cent. overweight has a slightly better tolerance than Case 42 with 34 per cent. overweight, and in the sixth decade Case 61 with 137 per cent. overweight has as good a tolerance as Case 63 with only 36 per cent. overweight. The amount overweight is, therefore, no index of the subject's tolerance. Such a conclusion is in disagreement with Joslin's statement (10), that the greater the obesity the greater is the subject's liability to become diabetic, but is in accordance with the observations of Labbé and Boulin (12) and of Allison (1), who favour the view that it is not the amount overweight, but the length of time the obesity has continued unchecked that influences the tendency to diabetes.

(3) *Relation of sugar tolerance to age.* This relationship is shown in Graph III where for the sake of clarity only the peaks of the tolerance

curves have been plotted according to the patient's age in each case. The line AB may be taken as representing the average height of the peaks (omitting the two groups of cases mentioned in section 1) and the interpretation of this line is that sugar tolerance diminishes with advancing years.

GRAPH III. Sugar tolerance in relation to age.

This is a fact which is already recognized Spence (17). Two factors thus require to be considered in making an estimate of an obese subject's sugar tolerance—age and the duration of the obese state.

In Graph III cases whose menopause is occurring or has occurred are indicated respectively by △ or ⊙. Case 38, the first of this group (marked by arrow) is 43 years of age. In only five cases to the right of No. 38 has no sign of the menopause yet appeared. It will now be seen that during the post-menopausal period the line AB continues to rise at the same rate as during the years before the menopause. The natural cessation of ovarian function at the menopause is not, therefore, associated with any accelerated falling off in sugar tolerance. Attention is drawn to this point in view of what will be said regarding sugar tolerance and ovarian function in the following section.

Ogilvie (13) showed that in thirteen out of nineteen obese subjects the islands of Langerhans were in varying degrees hypertrophied. Most of the subjects with hypertrophied islands were 49 years of age or upwards. A consideration of Graph III helps to an understanding of the sugar tolerance during these later years of life. The graph shows that after the age of

47 years eleven subjects had normal tolerance, while ten cases exhibited a subnormal tolerance (peak above 180 mg. per cent.) and three additional cases were frank diabetics. In the light of this knowledge it seems probable that the hypertrophy of the islets of Langerhans such as occurs in a considerable number of obese subjects is directed to maintaining a normal level of secretion for as long as possible.

(4) *Relation of sugar tolerance to ovarian function.* Attention may now be drawn to a relationship which has been observed between sugar tolerance and ovarian function. It will be noted that in Graph I there are six cases (30, 34, 36, 40, 46, and 54) each with a sugar tolerance considerably below that of the others with a history of obesity of similar duration. The diminished tolerance of these subjects is clearly shown in Graphs II a, II b, and II c. Not only are these cases outstanding in respect of their low sugar tolerance, but also because of the short duration of their obese condition and of the additional fact that each gives a history of diminished ovarian function. Thus Case 30 is a married woman, aged 24, who had a unilateral oophorectomy performed two years ago. Prior to the operation her menses were of the 7/28 type and the loss was average. Since the operation her menses have been half their former duration, now 3/28, and the loss has been scanty. Her obesity dates from the operation also. Case 34 is that of a married woman, aged 25, with markedly irregular and scanty periods, her loss amounting to one or two spots every 7–12 weeks. Case 46 is a married woman, aged 29, who has had no menstrual period since the birth of her sixth and last child three years ago. Her menarche occurred at the age of 17 years and her periods were regular (3–4/28) until they ceased in 1931. Case 54 is a married woman (nullipara), aged 29, whose menstruation has consisted of a scanty period lasting one or two days every 2–12 months. Case 40, the only one occurring in the fourth decade, is a married woman, aged 34, with six children. On account of severe haemorrhage before the birth of the sixth child she was sterilized by deep X-ray therapy eight months before she came under treatment for obesity. Lastly, Case 36, the only one in the fifth decade, is a married woman, aged 44, who on account of severe uterine haemorrhage two years ago was artificially sterilized by the insertion of radium.

It would thus seem that deficient function, premature exhaustion or destruction of the ovaries produces a definite lowering of sugar tolerance. Whether this lowering of tolerance occurs only in subjects who become obese, or whether it occurs also in subjects who remain thin, is a point yet to be determined. But if sterilization effects a marked lowering of sugar tolerance and at the same time initiates a state of obesity which is associated with further progressive diminution of tolerance then diabetes must be considered as a potential danger of such an operation.

Further evidence of a relationship between ovarian function and sugar tolerance is afforded by Case 48, an obese female diabetic, of the sixth decade. This elderly subject gives a history of twenty-seven years' obesity.

Her menopause occurred three years ago at the age of 54, and since then she states she has been losing weight.   In the year following her menopause she had an attack of pruritus, and a second attack occurred a year later. When she came under observation this year she complained of thirst and polyuria and her sugar tolerance curve, associated as it was with glycosuria, proves her to be frankly diabetic.   From what has already been said it may be deduced that after having been obese for twenty-seven years this elderly subject would have a much diminished sugar tolerance.   Her history suggests, moreover, that she became diabetic at the time of her menopause— in other words, cessation of ovarian function appears to have been associated with such an additional fall in tolerance that she was rendered definitely incapable of dealing with sugar.

On the other hand, attention has already been drawn in Graph III to the fact that natural cessation of ovarian function at the menopause does not influence sugar tolerance, the rate in fall of tolerance being the same as that in the years before the menopause.   This is, of course, what might be expected, for in most women cessation of ovarian function and menstruation is a more or less gradual process, so that the tissues and metabolism are given time to adjust themselves to the altering physiological conditions. As a rule it would therefore be unnatural to expect any demonstrable alteration in sugar tolerance.   But it would seem that as in Case 48 above cessation of ovarian function at the menopause does occasionally make manifest its influence on tolerance for sugar.

Raab (15) has found that after the injection of follicular and corpus luteum extracts normal women give sugar-tolerance curves which are definitely lower than the curves obtained before injection. Yuuki (19) finds that in guinea-pigs following ovariectomy there is increased glycosuria after intra-venous injection of glucose.   Finally, Gulick, Samuels and Deuel (3) conclude that in ovariectomized rats the liver glycogen is constantly higher than in normal females and that a reduction in hepatic glycogen is effected by theelin.

The work of the investigators quoted above suggests strongly that the ovary influences carbohydrate metabolism.   My own results support this conclusion and indicate that lack of some secretion of the ovary effects a lowering of sugar tolerance.

Summary and Conclusions

(1) In sixty-five obese subjects (all females except two) varying in age between 23 and 65 years and in percentage overweight between 14 per cent. and 137 per cent., sugar tolerance diminishes as the duration of the obesity increases.

(2) In about one-third of obese subjects there is a preliminary phase of increased sugar tolerance, but in the majority of cases tolerance for sugar is even in the earliest years normal.   Normal tolerance gives way later to deficient tolerance which ultimately expresses itself in diabetes.

(3) The hypertrophy of the islets of Langerhans which occurs in a proportion of obese subjects is probably directed to maintaining a normal level of insulin secretion for as long as possible.

(4) The sugar tolerance of the obese subject is not related to the amount of overweight.

(5) Sugar tolerance diminishes with advancing years.

(6) A relation has been observed between sugar tolerance in the obese subject and ovarian function.

REFERENCES

1. Allison, R. S., *Lancet*, Lond., 1927, i. 537.
2. Dunlop, D. M., and Murray Lyon, R. M., *Edinb. Med. Journ.*, 1931, xxxviii. 561.
3. Gulick, M., Samuels, L. T., and Deuel, H. J., *Journ. Biol. Chem.*, Balt., 1934, cv. 29.
4. Hagedorn, H. C., and Jensen, B. N., *Biochem. Zeit.*, Berl., 1923, cxxxv. 46 and cxxxvii. 92.
5. Hansen, K. M., *Disputations*, Copenhagen, 1923.
6. Harris, S., *Journ. Amer. Med. Assoc.*, Chicago, 1924, lxxxiii. 729.
7. Harris, S., *Endocrinology*, Glendale Cal., 1932, xvi. 29.
8. John, H. J., *Amer. Journ. Med. Sci.*, Philad., 1927, clxxiii. 184.
9. John, H. J., *Endocrinology*, Glendale Cal., 1934, xviii. 75.
10. Joslin, E. P., *Journ. Amer. Med. Assoc.*, Chicago, 1921, lxxvi. 79.
11. Kjer, K., *Acta Med. Scand.*, Stockholm, 1924–5, lxi. 159.
12. Labbé, M., and Boulin, R., *Bull. et mém. Soc. méd. hôp. de Paris*, 1925, 649.
13. Ogilvie, R. F., *Journ. Path. Bact.*, Lond., 1933, xxxvii. 473.
14. Petrén, K. A., *Diabetes-studier*, &c., 1923.
15. Raab, E., *Arch. Gynäk.*, Berl., 1930–1, cxliv. 284.
16. Root, H. F., and Miles, W. R., *Journ. Metab. Res.*, Morristown, N. J., 1922, ii. 173.
17. Spence, J. C., *Quart. Journ. Med.*, Oxford, 1920–1, xiv. 314.
18. Winans, H. M., *South Med. Journ.*, Birmingham, Ala., 1930, xxiii. 402.
19. Yuuki, H., *Arb. Med. Fakultät Okayama*, 1934, iv. 211.

616.34–008.337

TEN CASES OF IDIOPATHIC STEATORRHOEA [1]

By Th. E. HESS THAYSEN

(From the St. Elizabeth Hospital, Copenhagen)

With Plate 27

In a series of communications (50, 51, 53, 54, 55, 57) in which I have attempted to show that coeliac disease (coeliakie or intestinal infantilism), non-tropical sprue, and tropical sprue may be considered one disease, I (50, 53, 54) proposed that these three conditions should be grouped together under the one designation 'idiopathic steatorrhoea'. In their elaborate, and in many respects instructive, treatise Bennett, Hunter, and Vaughan (3) have opposed this view. They maintain that the majority of cases of non-tropical sprue described in the literature can be traced back to childhood and are therefore to be considered as late cases of coeliac disease. On the other hand, they are unable to deny that idiopathic steatorrhoea may make its first appearance in adult life in persons who have never been in the tropics (non-tropical sprue), but they regard such an event as an 'extremely rare occurrence'. They doubt whether coeliac disease and the extremely rare cases of non-tropical sprue are different diseases and collect these two conditions under the term 'idiopathic steatorrhoea' without any mention of the source and the original meaning of this term. Thus the term 'idiopathic steatorrhoea' in the sense of Bennett, Hunter, and Vaughan (3) does not include tropical sprue, which they think is a condition quite different from coeliac disease and non-tropical sprue.

The point of view of Bennett (3) and his collaborators gives rise to the following questions: (1) Do all or the great majority of cases of non-tropical sprue commence in childhood? (2) Are coeliac disease and non-tropical sprue different from tropical sprue?

The second question will be discussed briefly later on, as I have gone closely into the subject in several papers and in my monograph 'Non-tropical Sprue' 1932 (55). No single argument of real significance has been put forward by English writers against my contention that these conditions are one and the same disease, a view which has won general acceptance on the Continent and in the United States.

The first question, on the other hand, necessitates a somewhat detailed reference to Bennett, Hunter, and Vaughan's (3) paper. Their work is

---

[1] Received April 30, 1935.

based upon fifteen patients with idiopathic steatorrhoea whose disease, apart from that in one case (No. 12), they regard as having arisen during childhood, and they are considered therefore as examples of late recognized coeliac disease.[2]

First, a few remarks on the *diagnosis* of idiopathic steatorrhoea. It is well recognized that tropical sprue and coeliac disease often occur in patients who have previously suffered from disorders of the bowels. In the case of tropical sprue such disorder has most frequently been that of chronic dysentery. Exactly similar conditions are met with in non-tropical sprue and, as I have pointed out (55), such intestinal infections may be traced back frequently to childhood or to adolescence. These intestinal disorders have been regarded as predisposing to idiopathic steatorrhoea (coeliac disease, non-tropical and tropical sprue), but it has never been considered justifiable to conclude that these attacks of diarrhoea were the first stage of the disease in the patients concerned. Even if it be probable that idiopathic steatorrhoea may have an earlier stage of non-characteristic diarrhoea, the diagnosis cannot with certainty be made until the classical symptoms of the disease, namely, the fatty diarrhoea, is present. The fact that in Europe the disease in many instances remains so long undiagnosed is due, in my opinion, not to the fault of the patient's being unaware of the abnormal state of his stools, but to the physician's misunderstanding the significance of his symptom or his omission in not thoroughly questioning the patient on this point.

No doubt the greater part of Bennett, Hunter, and Vaughan's (3) cases of idiopathic steatorrhoea are cases of coeliac rickets, described by Parsons (37), Linder and Harris (26), Findlay and Sharpe (13), and others in adults or adolescents. The proof that this disease started in childhood as coeliac disease is in the majority of cases based only upon the case-histories. If the patient in question when a child has had fatty diarrhoea, rickets or osteoporosis, cessation of growth, and possibly tetany, there is then no doubt about the beginning of the condition as coeliac disease. On the other hand, this diagnosis remains uncertain when the main symptom of the disease, the fatty diarrhoea, has not been established. The fact that such symptoms as chronic diarrhoea, distended abdomen, cessation of growth, and eventually rickets, are quite frequently met with in childhood does not allow the conclusion that the patient has suffered from coeliac disease.

Bennett, Hunter, and Vaughan (3) are too prone to accept the presence of every kind of diarrhoea in childhood and adolescence eventually combined

---

[2] For the sake of clearness I propose to use the term coeliac disease in relation to idiopathic steatorrhoea occurring in children, non-tropical sprue for those cases in which the condition first became manifest during adult age in persons who had never been in the tropics, and tropical sprue where the condition first appeared in adult life in a tropical country. Such a division is a purely artificial one, as, in my opinion, all these groups represent the same disease which can arise in any age-period of life. Bennett, Hunter, and Vaughan's idiopathic steatorrhoea corresponds to the first two of the above groups.

with rickets and stunted growth as a proof of the existence of coeliac disease. As to the diagnosis 'consumptive bowels' in children, upon which these authors lay so much stress for the diagnosis 'coeliac disease', it may be remembered that this diagnosis, at any rate in Denmark, is frequently suggested in regard to children suffering from chronic diarrhoea and abdominal distension without the presence of steatorrhoea.

The anamnesic data upon which Bennett, Hunter, and Vaughan (3) have based their opinion that all their cases of idiopathic steatorrhoea but one can be traced back to infancy are in some cases not sufficiently convincing, and even if we give Bennett, Hunter, and Vaughan (3) the benefit of the doubt, two more cases (Nos. 11 and 15) have undoubtedly originated in adult life.

One serious objection to Bennett, Hunter, and Vaughan's (3) work lies in the fact that they have entirely omitted the examination of the nitrogen excretion in the faeces. This is of particular weight in considering those cases in which the blood-sugar curve showed a normal rise after ingestion of glucose, or where the form of the curve cannot be determined on account of the technique followed. In previous investigations recently confirmed by Anderson and Lyall (1), I (49) showed that the only means we possess of establishing the differential diagnosis between pancreatic and idiopathic steatorrhoea, in cases with a normal blood-sugar curve, is the estimation of the nitrogen excretion in the faeces, which is increased to a considerable degree in steatorrhoea of pancreatic origin [3]. This objection is valid in regard to Bennett, Hunter, and Vaughan's (3) Cases Nos. 11, 12, 15. These authors seem to be unaware of the fact that in pancreatic steatorrhoea one may find normal blood-sugar curves and disturbances of the calcium metabolism accompanied by tetany and skeletal abnormalities exactly similar to those observed in idiopathic steatorrhoea.

Passing on from the work of these authors to the cases of idiopathic steatorrhoea which form the basis of this communication, the series embraces one case which undoubtedly had its onset in Java as a typical example of tropical sprue and was referred to me by Professor Alsmeer with the diagnosis of sprue, six cases in which the affection commenced during the age-period 19–53 years (49) in patients who had never been in the tropics and which are to be classed therefore as cases of non-tropical sprue, and three cases of coeliac disease commencing during childhood.

From their clinical histories all six patients with idiopathic steatorrhoea, labelled non-tropical sprue, had been in good health during the early years of childhood and none of these showed any evidence of past rickets. Further, three cases (Nos. 2, 3, 5) had not suffered from diarrhoea before the commencement of their present illness, two cases (Nos. 1, 4) had a benign form of post-prandial diarrhoea during the age-period 10–14 years, after which time they had remained quite well for many years until their

[3] In Denmark some years ago 'English Disease' was a frequent diagnosis in relation to children who were constantly ailing and making no progress.

present illness began at the respective ages of 40 and 30 years. One patient only (No. 6) had suffered from diarrhoea when he was 12 years old. From 27–35 years of age he had had attacks of diarrhoea with aphthous stomatitis but apparently no steatorrhoea. His present illness commenced at the very earliest between the age of 27 and 35 years, probably between the age of 45–53. None of these six patients showed any evidence of past rickets.

Thus we find symptoms of intestinal disturbance occurring many years previous to their present illness in only three of these six cases. This figure agrees very closely with my previously published figures of non-tropical sprue (55). In tropical sprue Manson-Bahr and Willoughby (30) found a history of intestinal disturbance prior to their actual sprue in approximately 40 per cent. of 200 cases.

The three patients with idiopathic steatorrhoea to be regarded as cases of coeliac disease had suffered from diarrhoea of characteristic type since they were children. Case No. 10, with tropical sprue, had had dysentery and some form of poisoning accompanied by diarrhoea two and one years respectively before the commencement of his present illness.

The following Table from my monograph (55) shows the dates of the onset of the non-tropical sprue in relation to the ages of the patients.

TABLE I

Age of Patients at the Onset of Non-tropical Sprue

Age of patients	1–10	11–20	21–30	31–40	41–50	51–60
Number of cases	1	5	6	5	10	3

Nine cases of non-tropical sprue reported subsequently to the publication of the forementioned monograph and the six cases herein reported are noted in Table III. Completed with these additions Table I in its amended form is seen as under.

TABLE II

Age of Patients at the Onset of Non-tropical Sprue

Age of patients	1–10	11–20	21–30	31–40	41–50	51–60	61–70
Number of cases	1	6	8	13	11	6	0

From this table it is clear that in the majority of patients the disease commenced after the age of 21 years, viz. in thirty-eight of forty-five cases and in twenty-four among forty-five cases during the age-period 31–50 years.

The first question put forward on p. 359 may therefore be answered thus : There is no doubt that there are cases of idiopathic steatorrhoea to-day in which the disease started in adult life as non-tropical sprue, and further, that such cases are by no means so ' extremely rare ' as Bennett, Hunter, and Vaughan (3) would have us believe. Since the appearance of my monograph in 1932 I have had the opportunity of examining five fresh cases.[4]

[4] Dr. Douglas has told me that he has seen two cases of non-tropical sprue in Italy, and Dr. Engel has kindly informed me that seven cases of non-tropical sprue have been

I do not propose to discuss the main features of the disease, which in varying degree are common to all cases of idiopathic steatorrhoea. It is the objective findings (Table IV) which offer the greater evidence that we are concerned with one clinical entity.

TABLE III

Fifteen New Cases of Non-tropical Sprue Originating in Europe

Author.	Sex.	Age.	Approximate age at start of disease.	Notes.
Anderson and Lyall	M	34	33	Always in good health. No bowel trouble previous to one year before admission. No stomatitis.
Roux	M	65	56	At age of 54 diarrhoea of no special type lasting for some months accompanied by glossitis of two weeks' duration. Otherwise in good health.
Roux	M	37	33	History, given during the year previous to admission, of diarrhoea containing large amounts of fat for 18 months. No stomatitis.
Koolemans Beijnen	F	62	60	Diarrhoea 18 months previously accompanied by painful tongue.
Koolemans Beijnen	F	42	39	Previous health good. Attack of diarrhoea accompanied by painful tongue 2½ years previous to admission.
Brull	F	56	36	Well as a child and during adolescence, apart from a short attack of jaundice. Tetany. No stomatitis.
Thorfinn	F	36	26	Rickets when a child. No bowel trouble before the age of 26. Tetany. Stomatitis.
Engel	F	40	40	At age of 28 had diarrhoea, unable to work three weeks. At age of 38 recurrence of diarrhoea with blood in the stools. Fatty diarrhoea noticed two months prior to her admission. No stomatitis.
Colangiuli and Douglas	M	57	57	Family history negative. No disease worth mentioning before the present, which started five months prior to admission. Severe diarrhoea, paraesthesia and burning of the tongue.
Thaysen	M	44	40	Case 1. See Clinical Notes.
Thaysen	M	52	40	„ 2. „ „ „
Thaysen	M	31	23	„ 3. „ „ „
Thaysen	F	36	30	„ 4. „ „ „
Thaysen	F	41	19	„ 5. „ „ „
Thaysen	M	56	45–53	„ 6. „ „ „

The only published report of Curschmann, Dunner, and Bech's cases of non-tropical sprue is in a short reference. Marble and Bauer's case appears to me somewhat indefinite.

observed in Sweden, though only two of these have so far been published. A fresh case of non-tropical sprue was demonstrated by Giertsen before the Medical Society of Norway in 1934. In Lübeck Professor Hansen has observed four cases in the last six months.

TABLE IV

Clinical Symptoms in Ten Cases of Idiopathic Steatorrhoea

Case No.	Sex.	Age.	Steatorrhoea.	Stomatitis.	Anaemia.	Blood-sugar curve.	Basal metabolism %.	Pigmentation.	Diagnosis.
1	M	44	+ +	—	Hypochr.	Flat	107·4–106·5	+	Non-tropical sprue
2	F	52	+ +	—	Simple	,,	64·7–69·2	+	,,
3	M	31	+ +	+	,,	,,	130–131	+	,,
4	F	36	+	—	,,	,,	107–106·2	+	,,
5	F	41	+ +	—	Hyperchr.	,,	125·1–125·3	+	,,
6	M	56	+ + +	+	,,	,,	123·6–119·9	—	,,
7	M	35	+ +	+	Hypochr.	,,	104·4–100·3	?	Coeliac disease
8	F	24	—	+	,,	,,	110–119	+	,,
9	F	22	+ +	—	,,	,,	104–110·5	+	,,
10	F	35	+ +	—	Hyperchr.	,,	94·1–102·4	(+)	Tropical sprue

TABLE V

Metabolism of Fat and Protein in Six Cases of Idiopathic Steatorrhoea

	Weight of faeces in grm. per 24 hours.	Fat intake in 24 hours.	Fat output in 24 hours.	Loss of fat in %.	N-intake in 24 hours.	N-output in 24 hours.	Loss of N. in %.	Diagnosis.
1	210	232	30·5	13	18·4	2·4	13	Non-tropical sprue
2	400	142	39·2	27	12·3	2·3	19	,,
4	190	140	18·0	13	13·3	1·9	14	,,
5	110	155	23·0	15	15·36	1·0	7	,,
,,	475	137	59·8	—	—	3·2	—	,,
6	475	143	81·2	57	13·7	2·7	20	,,
,,	550	57	19·2	34	9·0	2·9	29	,,
7	350–500	—	—	—	—	—	—	Coeliac disease
8	160	143	14·1	10	12·1	1·2	10	,,

Metabolic Disturbances

The metabolic disturbances accompanying idiopathic steatorrhoea (Table V) undoubtedly constitute the central clinical feature of the disease. These are characterized by (1) The abnormal excretion of fat in the faeces. (2) The normal, or in rare instances slightly raised, nitrogen excretion in the faeces. (3) The flat blood-sugar curve. (4) The increased basal metabolism.

The combination of these four manifestations of altered metabolism, or of the three first-mentioned alone, does not occur in any other disease as far as we know, and is therefore pathognomonic of idiopathic steatorrhoea.[5] Concerning

[5] The only other disease, as far as I am aware, in which similar symptoms may be observed is tuberculous stricture of the small intestine, with steatorrhoea, anaemia, osteoporosis, and tetany. In one of my cases which was investigated the blood-sugar

their relative occurrence in the three sub-groups of idiopathic steatorrhoea, viz. intestinal infantilism (coeliac disease), non-tropical sprue, and tropical sprue, reference must be made to my monograph (55). The data recorded therein receive further confirmation from the results of the investigations mentioned below.

Fatty diarrhoea. (Table V.) The daily amount of the fat excreted varies as much as from 14 grm. to 81 grm. In the two cases (Nos. 4, 8) examined during a passive period, the fat-excretion was practically normal. In the most severe case (No. 6) the amount of fat excreted reached as high a figure as 81·2 grm. per day, or more than 50 per cent. of the ingested fat. I have omitted the figures of the total fat in the faeces showing the respective amounts of neutral fat, soaps, and free fatty acids, as these figures are of no great practical interest, and more particularly as they do not offer any elucidation at all of the cause of the diminished fat-absorption. I would like to point out once again that an exactly corresponding splitting of the faecal fat into free fatty acids and soaps is found in pancreatic as in idiopathic steatorrhoea.

In opposition to the generally accepted view that the steatorrhoea is due to a diminution in the absorption from the intestine, Bauer (2) and Moncrief and Payne (36) have maintained that examination of the blood showed no diminution in its fat-content fasting and a rise to a normal level after feeding with fat. In their opinion, therefore, the steatorrhoea is to be regarded as due rather to an excretion of fat by the bowel than to diminished absorption. This theory has already been disproved by Fanconi's (12) investigations in coeliac disease.

My assistants Lawaetz and Vogt-Møller (24) carried out the undermentioned estimation of the fat-content of the serum in the fasting state and after feeding with fat on some of the patients included in the present series. The fat-content of the serum was determined by Rückert's method. This method, according to Lawaetz and Vogt-Møller (24), does not permit the determination of the free cholesterin. They maintain, too, that the fractionation of the lipoids into neutral fat and phosphatides gives unreliable results. The figures of the total fat-content at the end of twenty-four hours, however, agree with the results of weight-analyses, if the fact that the free cholesterin cannot be determined by Rückert's method is taken into consideration. For the purpose of this investigation, therefore, Lawaetz and Vogt-Møller (24) have taken the figures of the total amount of fat at the end of twenty-four hours.

Examination of forty-six persons with normal fat absorption showed an average serum-lipoid content in the fasting state of about 540 mg. per

curve was not of the flat type according to my definition of the same. The basal metabolism was low. The patient suffered from attacks of colic-like pains in the abdomen accompanied by visible peristalsis. X-rays revealed the presence of strictures in the intestine, which condition was verified on the subsequent post-mortem examination.

cent. The lowest figure recorded was 300 and the highest 710 mg. per cent. In thirty-nine cases the fasting value lay between 387 and 645 mg. per cent. Following the administration by the mouth of 100 grm. olive oil to thirteen persons with normal fat absorption there was an average rise of 50 per cent. of the fasting value. In the five cases where this was low, viz. 430 mg. per cent. or under, there was noted an average rise of 90 mg. per cent. In three cases with a high fasting value of 645 mg. per cent. or over an average rise of 34 mg. per cent. of the fasting value was obtained.

TABLE VI

Fat Content in Serum after Giving 100 grm. Olive Oil

Case No.	Sex.	Age.	Fasting fat content.	Fat content after 2 hrs.	Fat content after 4 hrs.	Fat content after 6 hrs.	Rise in % of fasting value.	Diagnosis.
			mg. %	mg. %	mg. %	mg. %	%	
1	M	44	300	380	310	290	30	Non-tropical sprue
2	M	52	520	600	560	600	15	,,
4	F	36	450	540	690	665	52	,, *
6	M	56	345	365	385	475	38	—
7	M	35	350	—	—	—	—	Coeliac disease
8	F	24	250	300	340	340	27	,, †
10	M	35	595	532	790	615	33	Tropical sprue ‡

* Good period with almost normal fat absorption (daily fat excretion of 18 grm.).
† Examined after two days' diarrhoea with markedly increased fat excretion.
‡ Examined during his last stay in hospital, when the stools were normal in colour.

The seven cases of idiopathic steatorrhoea submitted to examination gave an average fasting value of about 400 mg. per cent. (the actual figures varying from 250 to 595 mg. per cent.), a figure considerably below that of normal persons (540 mg. per cent.). The responses to the ingestion of 100 grm. olive oil are shown in Table VI.

When we consider those cases tested during a period of their disease with diminished fat absorption (Nos. 1, 2, 6, 8, 10) we find that the rise in the blood fat-content is considerably below that of normal persons (15–38 per cent.) while the rise in the cases of the patient (No. 4) with low fat excretion is normal. It is true that the cases investigated are only few in number, nevertheless the figures obtained point to the steatorrhoea being due to a diminished fat absorption and not to an excretion of fat by the intestine. They show, too, that in the majority of the acute cases the value of the fasting fat-content lies about the lowest level for normal persons.

Nitrogen excretion in the faeces. (Table V.) The few investigations carried out in tropical sprue show normal conditions, viz. as much as 3 grm. in twenty-four hours (55), or a slightly increased amount (4 grm., A. D. Schmidt). In six cases of non-tropical sprue (55) I found a daily excretion varying from 2·96 to 0·85 grm., while Holst (18) in one case noted the slightly increased amount 3·63 grm., Anderson and Lyall (1) 1·9–2·5 grm., and

Brull (4) 2–3 grm. In the five cases of non-tropical sprue here reported the nitrogen excretion varied from 1·0 to 3·2 grm. per day (Table V). Normal or slightly higher nitrogen excretion values have also been found in coeliac disease (Lehndorff and Mautner (25), Macrae and Morris (28), McCrudden and Fales (32). The last-named workers do not ascribe the higher values to diminished absorption but to an increased secretion of intestinal juice and the emigration of leucocytes. Thus the faecal nitrogen excretion in idiopathic steatorrhoea is normal or slightly increased in a few cases.

Anderson and Lyall (1), however, in their Case No. 1 found a negative nitrogen balance of 4·9–5·2 grm. after the patient had been on a diet of 4·6 grm. nitrogen per day for forty-eight hours. This nitrogen intake is a very low one and it is not surprising therefore that the nitrogen balance was negative. In my experiments with a considerably higher nitrogen intake I obtained the figures shown in Table VII.

<div align="center">

TABLE VII

Nitrogen Balance

</div>

Case.	Nitrogen intake in grm.	Nitrogen excretion in grm.		Balance.
		Faeces.	Urine.	
				grm.
1	18·4	2·4	7·4	+8·6
2	12·3	2·28	11·6	−1·5
4	13·3	1·9	10·1	+1·3
5	15·36	1·0	9·68	+4·6
6	13·7	2·7	8·1	+2·9
—	9·0	2·9	6·5	−0·4
8	12·1	1·25	8·15	+2·7

From the above Table we see that among six patients with idiopathic steatorrhoea, viz. five cases of non-tropical sprue and one case (No. 8) of coeliac disease, five showed a positive nitrogen balance on a high nitrogen intake, while one case (No. 2) on a nitrogen intake of 12·3 grm. per day gave a negative balance of 1·5 grm. In the case of the patient No. 6 a second examination, while on a lower nitrogen intake than at the time of the first test, showed a small negative balance of 0·4 grm. It is therefore important to note that a relatively high nitrogen intake is essential for the maintenance of a positive nitrogen balance in patients with idiopathic steatorrhoea.

<div align="center">

The Flat Blood-sugar Curve

</div>

Since my publication (55, p. 94) the flat blood-sugar curve has been demonstrated as a constant finding in coeliac disease by Svensgaard (46), Haas (16), McLean and Sullivan (33), Macrae and Morris (28), and others. It has been observed in all ten cases of idiopathic steatorrhoea comprising the series here described (three cases of coeliac disease, six of non-tropical and one case of tropical sprue). Engel (10), Thorfinn (58), Brull (4), and Anderson and Lyall (1) found it, too, in their cases of non-tropical sprue.

In the fifteen cases comprising Bennett, Hunter, and Vaughan's (3) series, a flat blood-sugar curve was noted in nine (Nos. 1, 3, 6, 7, 8, 9, 10, 13, 14) and a normal curve in two cases (Nos. 4, 5). The method adopted by these authors precludes any expression of opinion on the shape of the curve in their remaining four cases.

My investigations in regard to the form of the blood-sugar curve in other types of steatorrhoea support the assumption of Macrae and Morris (28) that this flat blood-sugar curve is not found in other types of fat-diarrhoea but only in those of idiopathic steatorrhoea. The determination of the flat curve, therefore, is a point of extreme significance in the differential diagnosis of the condition. Its occurrence in both tropical and non-tropical sprue and in coeliac disease affords support of considerable weight to my view of these three conditions being one and the same disease. Bennett, Hunter, and Vaughan (3) entirely evade this question in their study.

In a previous paper (55) I asserted that the flat blood-sugar curve is observed most frequently during the bad periods of the disease and that it may be replaced by a normal one during the good periods. At the same time the investigations have shown that a flat curve may also be found during periods of normal fat absorption (see also Case No. 8). This observation has been confirmed by Svensgaard (46) and Macrae and Morris (28). Again, a normal curve may be observed during bad periods, even when the same patient has previously shown a flat curve at such times (55). It is evident, therefore, that there is no constant relation between the diminution of fat absorption and a flat blood-sugar curve.

In my monograph (55, p. 102) and in previous communications (50, 52) I maintained that the flat curve can hardly be due to a diminished absorption of glucose but rather to a disturbance of the blood-sugar regulation. This hypothesis was based on the following observations: (1) Following intravenous injection of glucose, patients with flat blood-sugar curves show a flatter curve than do normal persons. (2) After the administration of glucose by the mouth the respiratory quotient rises, as in normal persons, to 1 or to about 1. (3) On a diet rich in carbohydrates the respiratory quotient is higher than on a mixed diet, as in the case of normal persons.

Macrae and Morris (28), without making a single experiment to disprove these observations, state that my results are 'equivocal'. The view that the flat blood-sugar curve is dependent upon diminished glucose absorption seems to be generally accepted by English physicians, so much so that a text-book teaches the occurrence in sprue of a diminished ability to absorb glucose.[6]

Further, Macrae and Morris (28) have misunderstood Cathcart and Markowitz's (6) interpretation of the respiratory quotient suggested by their experiments and upon which the first-named writers support their criticism of my explanation of the flat blood-sugar curve. Cathcart and Markowitz (6) do not assert as do Macrae and Morris (28) 'that the value of the respiratory

[6] See article 'Sprue' in Price, *A Textbook of the Practice of Medicine*, 1933, p. 624.

quotient is really the resultant of *all metabolic* processes', but express their belief that ' the non-protein respiratory quotient represents not a combustion quotient but the algebraic sum of the transformation of carbohydrates into fat and vice versa, plus the oxidation of the carbohydrate for energy purposes'. Even if this supposition is proved to be correct, still the normal rise of the respiratory quotient after glucose administration and the higher quotient after a carbohydrate meal in patients with flat blood-sugar curves signify a normal reaction towards the ingestion of carbohydrates, which presupposes a normal absorption of the same substance.

According to Macrae and Morris (28), it is merely a question of the absorption of glucose at a slower rate than in normal persons. Against this view is the fact that about 50 per cent. of the flat blood-sugar curves fall to the fasting level or even lower in normal time, viz. 2–2½ hours after the ingestion of glucose. This is shown clearly in Macrae and Morris's (28) own curves.

The fact that glucose is one of the most readily absorbed substances is a point in favour of my interpretation of the flat blood-sugar curve. In a case of gastro-colic fistula with marked steatorrhoea and creatorrhoea I found a normal blood-sugar curve after giving glucose. Snapper (45) has made a similar observation. Finally, I have observed a normal curve in a patient who had undergone a resection of four metres of the small intestine for intestinal infarction and whose ability to digest fats and protein was considerably diminished in consequence. It is clear, therefore, that only very severe and extensive damage to the intestinal tract can hinder glucose absorption, such as has not been demonstrated in idiopathic steatorrhoea. Against the theory of the dependence of the flat blood-sugar curve upon a diminished or delayed absorption of glucose, too, are the excellent results following a pure carbohydrate diet in coeliac disease (Haas, 16).

Until further evidence to the contrary is forthcoming I therefore maintain that the flat blood-sugar curve is due, not to deficient absorption, but in all probability to a disturbance in the regulation of the blood-sugar, since the glycogen storage (particularly in the liver) appears to be normal, as is accepted too by Macrae and Morris (28). Bennett, Hunter, and Vaughan (3) associate themselves with Macrae and Morris's (28) somewhat meaningless criticism of my experiments and explanation of the flat blood-sugar curve, while they state, however, ' We feel it would be premature to assume that the flat blood-sugar curve must be accepted as evidence of an actual derangement of the absorptive function of the intestinal mucosa.'

Basal Metabolism

The alterations observed in the basal metabolism in idiopathic steatorrhoea do not appear to have aroused any interest. In my monograph (55, p. 107) I mentioned in detail the observations to hand at that date (1932). In tropical sprue an increased rate was observed by Krjukoff (23) in 1 of 7 and

by Kassiersky (20) in 17 of 23 cases ; McCrudden and Fales (32) and the author had found the basal metabolic rate raised (+40 per cent.) in coeliac disease. In non-tropical sprue a normal rate was recorded in 5, a low in 3, and an increased rate in 7 cases.   I drew attention to the further observation that the increased rate of basal metabolism was lower or normal during the good periods of the disease.   In the 6 cases of non-tropical sprue in the present series (Nos. 1–6) the basal metabolism was found as high as 130–1 per cent. in 3 cases (Nos. 3, 5, 6), normal in 2 (Nos. 1, 4), and low (64·7–65·2 per cent.) in 1 case (No. 2).   The two cases with a normal rate were enjoying a relatively good period of their disease at the time of the test.   The same was the case in regard to the three patients (Nos. 7, 8, 9) with coeliac disease, while the patient with tropical sprue (No. 10) showed a normal rate during a bad period.

Case No. 6, with an increased rate of 125 per cent. during a bad period, showed nine months later a normal basal metabolic rate of 103–4 per cent. following a considerable improvement in his condition.   I have discussed the explanation of the increased basal metabolism in my monograph (55, p. 113) and know of nothing fresh to add upon the subject.   It is a remarkable fact that persons manifesting such pronounced wasting, as do patients with idiopathic steatorrhoea, show an increase rather than a decrease in their basal metabolism.   It is the increased rate of the basal metabolism, the diminished fat absorption, the normal or slightly increased nitrogen excretion in the faeces, and the flat blood-sugar curve which constitute the characteristic manifestations of the deranged metabolism in idiopathic steatorrhoea.

Calcium Metabolism

Herter's work has shown that children with coeliac disease frequently have a negative calcium balance, while Scott (43) was the first to determine the presence of disordered calcium metabolism in tropical sprue and Holmes and Starr (17) a similar disturbance in non-tropical sprue.

A disordered calcium metabolism has thus been found in all three sub-groups of idiopathic steatorrhoea and is accompanied by changes in the phosphorus metabolism. *It is necessary to point out, however, that the abnormal calcium metabolism observed is not peculiar to idiopathic steatorrhoea.* Exactly similar sequences of a disturbed calcium metabolism, viz. hypo-calcaemia, tetany, spontaneous fractures, and osteoporosis, have been noted in pancreatic steatorrhoea by Holst (19), whose observations I am able to confirm.   A woman, aged 60 years, with fatty diarrhoea of pancreatic origin and diabetes, exhibited tetany, hypocalcaemia, hypophosphataemia, numerous spontaneous fractures with calcium-deficient callus on healing, very pronounced osteoporosis, and commencing osteomalacic deformity of the pelvis.

The development of skeletal changes in dogs with a biliary fistula and subsequent steatorrhoea was noted by Pawlow several years ago. His observations have been confirmed by Seidel (44) in the case of a woman with a biliary fistula, who exhibited numerous fractures which healed with callus formation resembling connective tissue. Schmorl (44) examined this same patient very thoroughly and described the bone changes present as resembling those of osteoporotic osteomalacia. The more recent experimental work of Dietrich (9), Tammann (47), and Loewy (27) has supported the observation that in animals with biliary fistula there occurs an osteoporosis accompanied by fractures healing with connective tissue-like callus. Tammann (47) showed that the administration of ergosterol to these animals diminished the demineralization of the bones and prevented the development of osteoporotic osteomalacia. Dietrich (9) and Loewy (27) observed an hypertrophy of the parathyroid glands in their animals submitted to experiment, the cause and significance of which remains unexplained.

The good effect of giving ergosterol or of exposure to quartz-lamp irradiation suggests that this disordered metabolism is to be regarded as evidence of D-hypovitaminosis. *Hence it follows that the skeletal changes, which are the clinical manifestations of the abnormal calcium and phosphorus metabolism, are to be interpreted as merely a complication of the primary disorder, namely, the diminished fat absorption, apart from any consideration of its pathogenesis.*

It is very important that this point should be made quite clear. The sequelae of the abnormal calcium and phosphorus metabolism may in some instances be so pronounced and stamp the clinical picture so markedly that they give it the appearance of a disease entirely different from that presented by other cases where such sequelae are absent or present only in lesser degree. I am inclined to believe that Bennett, Hunter, and Vaughan (3) have not been quite clear about the relative significance of these clinical signs and that they have thus gained the impression that the cases of idiopathic steatorrhoea described by themselves differ entirely from tropical sprue, where the disordered calcium metabolism appears to be less conspicuously expressed in the skeletal system. The question of the skeletal changes in tropical sprue requires further investigation. A point worthy of notice is the striking manner in which rachitic and osteomalacic changes stamp Bennett, Hunter, and Vaughan's (3) cases of coeliac disease, when compared with the cases described herein (see Fig. 4) and with those reported by Gjørup (15), in all of which the rachitic changes, generally speaking, were much less pronounced. The difference can perhaps be explained by the greater incidence and severity of rickets (osteomalacia) in England than in Denmark. It is not without reason that on the Continent rickets is designated 'the English disease'. In several cases of coeliac disease reported from Germany by Koll (21) the skeletal changes present were also less pronounced than in Bennett, Hunter, and Vaughan's (3) patients.

Of the present series five cases showed definite osteoporosis, and two

patients (Nos. 2, 4) have developed a mild degree of kyphosis of the dorsal vertebrae (Table IV).

Examination of the CaO of the faeces and urine reveals the excretion of CaO in greater amount in the faeces. The calcium balance (Table VIII) in

TABLE VIII

Case No.	CaO in food. grm.	CaO excretion. grm.		CaO balance. grm.	CaO in serum. mg. %	P in serum. mg. %	CaO in serum after treatment.	Osteoporosis.	Rickets.	Tetany.	Diagnosis.
		Faeces.	Urine.								
1	2·52	2·52	0·02	−0·02	8·6	—	10·7	—	—	—	Non-tropical sprue
2	2·12	2·16	0·04	−0·02	8·5	—	11·5	+	—	—	,,
3	—	—	—	—	?	?	—	?	—	+	,,
4	2·16	1·5	0·04	+0·62	11·05	3·2	11·5	—	—	—	,,
5	1·9	1·58	0·04	+0·28	8·8	—	10·0	—	—	—	,,
6	1·5	1·50	0·12	−0·12	6·0	2·5	11·2	+	—	+	,,
,,	1·6	1·5	0·10	±0	—	—	—	—	—	—	,,
7	—	—	—	—	11·8	—	11·0	+	+	—	Coeliac disease
8	2·02	0·78	0·04	+1·2	10·4	—	11·8	+	+	+	,,
9	—	—	—	—	8·95	—	—	+	+	—	,,
10	—	—	—	—	9·7	—	—	—	—	—	Tropical sprue

the cases examined showed figures varying from −0·12 to +1·2 in twenty-four hours. Only in the Cases Nos. 4 and 8, which were tested in a good period with low fat excretion (see Table V), was the absorption of CaO sufficient to cover the daily consumption, which may be estimated at as much as 0·5–1·5 grm. In the Cases Nos. 1, 2, and 6 examined during a period of relatively high fat excretion the CaO balance was negative, the greatest deficit was found in Case No. 6 with the highest fat excretion. The CaO content of the serum was low in one case (No. 6) during an attack of tetany, but was raised to the normal after treatment with calcium and ergosterol. In four cases (Nos. 1, 2, 5, 9) the CaO content of the serum was at the lower level of normal.

The Table shows that a daily intake of up to 2·5 grm. CaO does not always ensure a sufficient resorption in cases with marked steatorrhoea.

In Brull's (4) case an adequate calcium absorption of 1·5 grm. was not obtained until over 2 grm. CaO was added to the food. Thus it is of the greatest importance to give an adequate amount of both CaO and phosphorus and ergosterol to ensure absorption.

The calcium absorption in Case No. 8 (coeliac disease) was normal, inasmuch as the approximate amount of 1·2 grm. contained in the diet was absorbed. The patient at the time of the test was in a good period with almost normal fat and with normal nitrogen absorption and a flat blood-sugar curve.

Anaemia

As I have previously stated (55, p. 47) a hyperchromic anaemia had been observed in 22 out of 32 cases of non-tropical sprue, with a colour index of

1·1 or higher.   Among the thirteen cases of non-tropical sprue (Roux (39) does not give the figures of the blood examination in his two cases) collected in Table III a hyperchromic anaemia was found in eight (Koolemans Beijnen (22), Anderson and Lyall (1), Brull (4), Thorfinn (58), Engel (10), Colangiuli and Douglas (8), and Nos. 5, 6, Table IV).   A hypochromic or simple anaemia (colour index 0·9–1·0) was demonstrated in five cases.   Thus we find a total of 30 patients with hyperchromic anaemia among forty-five cases of non-tropical sprue, or approximately 70 per cent.   Among 182 cases of tropical sprue 109 (60 per cent.) had hyperchromic anaemia (see 55, p. 50).   The incidence of this type of anaemia is thus equal in tropical and non-tropical sprue.

All three patients of the present series in whom the disease had commenced in childhood as coeliac disease had an anaemia of hypochromic type.

The occurrence of anaemia of hypochromic type in cases of coeliac disease in Bennett, Hunter, and Vaughan's (3) series and in my three cases herein described agrees with the findings of earlier observers.   Hotz and Fanconi's (12) investigations, however, have shown that typical hyperchromic anaemia may be found in coeliac disease.   The greater incidence of hypochromic anaemia in this affection does not therefore signify any fundamental difference between coeliac disease and sprue, but rather the expression of a special reaction on the part of the juvenile organism towards the causative agent of the anaemia.   The occurrence of hyperchromic anaemia in children is recognized to be extremely rare.

It is a matter of general experience that the hyperchromic anaemia in tropical and non-tropical sprue can dominate the clinical picture to such an extent that the condition has been wrongly diagnosed as one of pernicious anaemia.   In two of my cases (Nos. 3, 8) the hypochromic anaemia had been so pronounced during an early stage of the disease that the patients had been treated for simple achylic anaemia, since the abnormal appearance of the stools had remained undetected.   In such cases, however, the relative lymphocytosis, noted in six among my seven cases of idiopathic steatorrhoea with hypochromic anaemia, can be a guide to the correct diagnosis, since simple achylic anaemia generally shows a normal leucocyte formula (Wintrobe and Beebe (60), Meulengracht (34)).

In England there have been published two helpful papers towards the explanation of the hyperchromic anaemia observed in idiopathic steatorrhoea. Fairley and Kilner (11) found a pronounced megalocytosis in four cases of gastro-jejunal fistula with steatorrhoea.   In the light of the observation of Wills on the effect of marmite upon tropical megalocytic anaemia Vaughan and Hunter (59) administered marmite to two cases of idiopathic steatorrhoea with megalocytic anaemia and noted a pronounced reticulocyte response accompanied by considerable improvement of the anaemia.   Castle and Rhoads (5) had the same experience in a few cases treated with autolysed yeast.   In my patient with tropical sprue here described, who during $2\frac{1}{2}$ months prior to his admission to hospital had been treated with liver, I found a mild hyperchromic anaemia.   Following the administration

of yeast (three tea-spoons daily) there was only a slight rise in the number of reticulocytes from 14 to 20 per cent., while the haemoglobin rose from 74 to 101 per cent. and the red cells from 3·34 to 4·82 millions. Subsequently he took yeast regularly, and in spite of a relapse of his disease the blood condition was found to be normal: Hb 98 per cent. r.b.c. 5·06 millions. These observations seem to point to some connexion between vitamin B and the hyperchromic anaemia. In such cases the vitamin B acts probably as an ' extrinsic factor '.

In a previous communication (1928) I drew attention to the fact that an untreated hyperchromic anaemia may be replaced by a hypochromic anaemia in the same patient on his passing over into a good period, and that a hypochromic may be replaced by a hyperchromic anaemia during a bad period. I have recorded a similar alternation of the anaemia from the hypo- to a hyperchromic type, or vice versa, in ten among thirty-two cases (55, p. 43). None of these same had been treated with liver. In regard to the present series I did not definitely determine this alternation, though it may perhaps have taken place in the case of patient No. 3. All the cases showing hyperchromic anaemia received liver treatment. In Brull's (4) case the anaemia alternated between the simple and hyperchromic types thus:

5.8.32	Hb 82 per cent.	R.B.C. 4·2 Mill.	C.I. 0·98
8.2.33	,, 85 ,, ,,	,, 3·25 ,,	,, 1·30
25.4.33	,, 80 ,, ,,	,, 4·4 ,,	,, 0·9

There is no mention that this patient received liver or marmite.

If it be correct that the hyperchromic anaemia is due to deficient absorption of an ' extrinsic factor ', this alternation in the morphological picture of the anaemia during the poor and good periods of the disease becomes more comprehensible.

Hypotension

In a previous summary of the blood-pressures observed in non-tropical sprue I have recorded a systolic blood-pressure of below 100 mg. Hg in seven of thirteen cases (55, p. 57). The corresponding figures in relation to six cases of my present series were:

No. 1. (1930) 135/90, (1932) 130/85, (1933) 115/65, (1934) 100/50.

,, 2. (1933) 110/75, (1934) 95/45.

,, 3. (1932) 110/75.

,, 4. (1934) 95/50, 90/50.

,, 5. (1932) 110/60, 100/50.

,, 6. (1933) 75/45, 75/45, 95/55, (1934) 95/55, 85/50.

In these six cases, too, the average blood-pressure was low, figures below 100/60 being noted in three patients. The first case demonstrates very clearly how the blood-pressure falls with the prolongation of the disease, while Case No. 6 shows the rise during the relatively good periods. I have

observed the same variation in another patient whom I had previously had under my care, whose blood-pressure prior to the commencement of the illness had been 155/95 and which fell during a severe attack of steatorrhoea to 90/60, to rise again during a good period of comparatively long duration to 180/120.

Anderson and Lyall (1) noted a blood-pressure of 95/50 in one of their patients who had been ill only about twelve months. In Brull's (4) case, with the illness of twenty years' duration, the blood-pressure was 95/60 and rose during a period of improvement to 125/75. Thorfinn's (58) patient had a blood-pressure of 95/60. In the three cases of idiopathic steatorrhoea in my present series commencing in childhood as coeliac disease the figures were: Case No. 7 100–95/65, No. 8 100/65, and No. 9 100/65, the blood-pressure in all these three patients being thus at the lowest limit of normal.

Pigmentation

The occurrence of abnormal pigmentation in chronic cases of idiopathic steatorrhoea is a well-recognized observation. In tropical sprue this feature may be so extensive as to suggest the diagnosis of Addison's disease, as it did in the case of non-tropical sprue reported by Brull (4). I have discussed the frequency and the possible pathogenesis of this pigmentation in my monograph (55, p. 57). Among the ten cases of idiopathic steatorrhoea comprising my present series seven exhibited pigmented patches (Table IV). In the one case of tropical sprue it is probable that the pigmentations had been more pronounced at an earlier stage. In seven cases (Nos. 1, 2, 3, 4, 5, 8, 9) the pigmentation was distributed over the face, and was noted most frequently upon the forehead and then on the nose, spreading as in pellagra to the region below the eyes. Some cases showed pigmented patches on the chin and neighbouring parts of the cheeks; in another (No. 5) the lesions appeared as pigmented streaks from the angles of the jaw to the cheeks. In all cases the pigmentation showed a symmetrical distribution, was yellowish-brown in colour, and sharply defined from the normal skin. All seven patients stated that the patches of pigmentation were more pronounced during the bad periods of their disease and were less obvious during the good periods, while they never entirely disappeared. Sunlight, too, was stated to accentuate the pigmentation. In two cases (Nos. 3, 8) there were also symmetrical patches of pigmentation on the extremities (see Fig. 5). In no instance, however, was there any evidence of hyperkeratosis over the pigmented areas. The distribution of the pigmentation was so characteristic that I was able, in the case of the patients Nos. 4 and 9, to suggest the condition of idiopathic steatorrhoea from this observation.

In its appearance and symmetrical distribution the pigmentation is very like that occurring in pellagra. In one case (No. 4) there was a patch of black-brown pigmentation with hyperkeratosis on the left elbow very similar

in appearance to pellagrous dermatitis, while the lesions on the face were not accompanied by hyperkeratosis. In a previous communication (56) I described these peculiar hyperkeratotic patches of pigmentation on the elbows in definite pellagra and in other cases where such patches resembled pellagrous dermatitis. I regard this pigmentation as evidence of a B-avitaminosis, a view confirmed by the experiences of Schiødt (42). In this connexion the occurrence of pellagroid skin changes in Bennett, Hunter, and Vaughan's (3) Case No. 8 is of interest.

Stomatitis

Low (7) reported the incidence of stomatitis in tropical sprue to be approximately 67 per cent., having observed its occurrence in 101 of his 150 cases. In the majority of the remaining cases there was a history of such stomatitis at an earlier date. Only 9 per cent. of his patients had never suffered from stomatitis. In non-tropical sprue glossitis of typical appearance was found in 26 of 32 cases (55 p. 26). In the 15 cases of non-tropical sprue summarized in Table III glossitis or stomatitis was noted in 6 instances, while 2 patients have had stomatitis at an earlier date to the time of examination. The presence of glossitis at the time of examination has thus been determined in 32 out of 47 cases, i.e. in about 70 per cent. Stomatitis then appears to occur as frequently in non-tropical sprue as in tropical sprue.

In regard to the three cases of coeliac disease (Nos. 7, 8, 9) a very pronounced glossitis was observed in Case No. 8 and a mild glossitis in Case No. 7, while the third patient, No. 9, had no glossitis, nor had she ever suffered from a painful tongue. Concerning Case No. 8 the glossitis, which had troubled the patient for many years during the bad periods of the disease, cleared up entirely under treatment with three teaspoonfuls of yeast daily and 'spinatin' (containing vitamins A, B, and some C) without any recurrence during an attack of diarrhoea. Schaap (40) noted the presence of a typical sprue-glossitis in coeliac disease, and from my own experience I can confirm his observations. The incidence of stomatitis in coeliac disease is, however, considerably lower than in tropical and non-tropical sprue, the reason for this difference being at present unexplained.

Avitaminosis

A priori it would seem probable that idiopathic steatorrhoea would predispose to the onset of a- or hypovitaminosis of the fat-soluble vitamins (A, D, and E). Typical avitaminosis A, however, appears to be of rare occurrence. Fanconi (12) observed xerophthalmia in coeliac disease, and hemeralopia was noted in one of the cases (No. 3) of non-tropical sprue herein reported. It is possible that more careful examination will reveal a greater incidence of avitaminosis A. Taking into consideration the fact

that the absorption of vitamin A is dependent upon the fat-content of the intestines, it is reasonable to suggest that the infantilism in coeliac disease is in part, at any rate, a symptom of hypovitaminosis A.

It is generally agreed that a hypovitaminosis D is a prominent cause of the abnormal calcium metabolism which is observed as an almost constant feature of coeliac disease, is frequent in non-tropical sprue, and occurs, too, in tropical sprue. Among the earlier cases of non-tropical sprue, in most instances following deficient examination or no examination at all, there were seven exhibiting definite osteoporosis (55, p. 78). Osteoporosis was noted in two out of the five cases examined (Table VIII). All three cases of coeliac disease showed osteoporosis.

How far the diminished sexual impulse occurring in idiopathic steatorrhoea may be ascribed to an avitaminosis E is a question which has not been investigated.

Avitaminoses of the water-soluble vitamins B and C are also found. It is probable that such conditions are to be regarded as of endogenous origin, occasioned by a disturbance of absorption as the avitaminoses of the fat-soluble vitamin group.

The occurrence of avitaminosis in tropical sprue appears to be quite definite (Holst (18)). Pichard (38) has reported a beri-beri-like polyneuritis complicating a case of sprue which had started in Algiers. Rud published a case of unrecognized coeliac disease which had previously been treated for a polyneuritis of the beri-beri type. In my Case No. 2 (non-tropical sprue) the patient developed a paresis of the lower limbs, diagnosed by a neurologist as polyneuritis, which cleared up *pari passu* with an improvement in the intestinal conditions.

It is well recognized that in America sprue and pellagra are not infrequently noted together, and that this complication has occasioned a wrong diagnosis in regard to many cases. Froboese and Thoma (14), in Germany, described a case which they regarded as one of sprue complicated by pellagra. In my own opinion the case was one of pellagra showing rather fatty stools as an occasional complication. Hiemcke has described a case of tropical sprue with pellagroid pigmentation. In one of Bennett, Hunter, and Vaughan's (3) cases (No. 8) pellagra-like changes were observed in the skin of the limbs.

There is thus no doubt that avitaminoses of the B group may complicate idiopathic steatorrhea, and it would therefore be likely that hypovitaminosis B occurs with even greater frequency. As previously stated, Vaughan and Hunter's (59) and Castle and Rhoad's (5) experiments in relation to the effect of vitamin B upon the hyperchromic anaemia points to the interpretation of the anaemia as a *possible* manifestation of hypovitaminosis B. I am inclined, as I have already mentioned, to correlate the brownish patches of pigmentation, so frequently to be noted, with a hypovitaminosis B on account of their symmetrical distribution and sharp definition, which resemble the features of the pigmented patches seen in the

skin of pellagrins. In the case of coeliac disease described by Rud areas of pigmentation were observed on the face, and on both sides of the abdomen symmetrically distributed and sharply defined. The patient, as already stated, had a beri-beri-like polyneuritis. Tannbauser (47 a) is a staunch supporter of the view that the pigmentations observed in pellagra, outside the areas of dermatitis, is due to B_2 avitaminosis. Recent investigations of Vogt-Møller (61) have shown that mice placed on a fat rich diet that produced steatorrhoea require a considerable surplus of vitamin B_2 to prevent the development of pellagra-like symptoms.

Whether the glossitis stands in some relation to a hypovitaminosis is a question at present undecided. The observations quoted on p. 376 would seem to support such a supposition.

Fanconi (12) noted typical scurvy in a case of coeliac disease, and Gjørup's (15) case of coeliac rickets also showed scurvy as a complication. One of my patients with coeliac disease (No. 8) had suffered from very severe bleeding from the bowel, of unrecognized aetiology, and showed later a tendency to develop spontaneous subcutaneous ecchymoses. There was no scurvy-like stomatitis, but a glossitis typically like that of sprue. The haemorrhagic tendency, however, can be regarded in all likelihood as evidence of hypovitaminosis C.

Morawitz has described a case of chronic colitis with chloasma-like pigmentation, which disappeared on a diet (oranges) rich in vitamin C. He therefore regarded the patches of pigmentation as being due to a hypovitaminosis C.

Megacolon

One of the most conspicuous clinical features of idiopathic steatorrhoea is the large abdomen with pronounced tympanites. The distension of the abdomen is due, without doubt, in part to the thin abdominal wall. The filling of the intestines with gas is compensatory to the loss of the intra-abdominal fat. During the last few years, however, a dilatation of colon has been recognized in coeliac disease (Miller (35), Taylor (48), Linder and Harris (26)), and the same observation has been recorded by Holmes and Starr (17) in a case of non-tropical sprue. In tropical sprue one would expect to find the same conditions (see below). Bennett, Hunter, and Vaughan (3) examined eight cases of idiopathic steatorrhoea and noted an abnormal dilatation of the colon in six of the same, with the condition affecting only the descending colon in the less pronounced and the entire colon in the more severe cases. They consider that a relation is to be found between the functional activity of the intestine and the dilatation of the colon, inasmuch as they observed no dilatation of the colon in the two cases in which the diarrhoea was a marked feature. On the other hand, only one patient with megacolon had diarrhoea. In five of the ten cases of idiopathic steatorrhoea comprising the present series, the shadow of the colon was examined after the injection of an opaque enema. In one case (No. 4) showing

no distension of the abdomen the large intestine was normal, and it was specially noted that the sigmoid flexure was of normal length. In contrast to this last case a dilatation of the descending colon and sigmoid flexure, the latter being very long, was noted in three cases of non-tropical sprue (Nos. 1, 3, 6). The transverse and the ascending colon were of normal width even in the most pronounced case (No. 3), which required 3 litres of the opaque enema to fill the intestine. In one case of tropical sprue (No. 10), with quite moderate distension of the abdomen, there was likewise a long sigmoid flexure, which, together with the descending colon, was dilated and showed poorly marked sacculation, while the transverse and the ascending colon were normal.

In agreement with Bennett, Hunter, and Vaughan's (3) investigations we may assume that the dilatation of the colon frequently starts in its distal portions, the descending colon and the sigmoid flexure, whence the process may spread to the proximal parts. The latter, however, can maintain their approximately normal width for a long time, as is shown by Case 3. A second characteristic feature is the poorly marked secular pattern of the colon, even in the sections of the large intestine showing no dilatation. This circumstance appears to me to suggest that the primary cause of the dilatation of the colon is to be sought in a derangement of its innervation producing an atony of the bowel. In association with the low blood-pressure this disturbance may be regarded as an expression of a lowered vagotonus induced possibly by some damage to the suprarenal glands. That the large motions and extensive development of gas contribute to the dilatation of the colon would seem probable.

I am inclined to explain the relation between the state of the intestinal function (diarrhoea, no diarrhoea, and eventual constipation) and the dilatation of the colon, by assuming that there occurs a primary dilatation of the colon which enables the faeces to be retained longer, and the diarrhoea in this way to be avoided. According to this theory the dilatation of the colon, arising upon a nervous basis, is the primary condition. The possible occurrence of diarrhoea in spite of the dilatation is well known in other forms of dilatation of the colon. Bennett, Hunter, and Vaughan's (3) observations, as well as my own, support this assumption.

In this communication my aim has been partly to offer a contribution to the clinical study of idiopathic steatorrhoea and partly to meet certain objections against the view which I have advanced that coeliac disease, non-tropical sprue, and tropical sprue are one and the same disease. I have not been able to go into all the points raised, and must, to a large extent, refer those interested to my previous papers and to my monograph (55), where they will find the subject discussed fully. In this paper I believe I have satisfactorily countered Bennett, Hunter, and Vaughan's (3) contention that non-tropical sprue is an ' extremely rare occurrence ' and that the majority of the cases of the disease described as such in the literature are to be

regarded as late diagnosed examples of coeliac disease.   Bennett, Hunter, and Vaughan (3) have, however, reached the opinion that it is a matter of doubt as to whether non-tropical sprue is not the same as coeliac disease.   These authors, then, appear to be so far in agreement with me, but they reject, on the other hand, as does also Manson-Bahr (29), the idea of coeliac disease and non-tropical sprue being the same disease as tropical sprue.

No one denies that in their clinical features the three diseases resemble one another very closely, and no one denies that the same metabolic disturbances are found in all three conditions.   The less frequent occurrence of glossitis and hyperchromic anaemia in coeliac disease compared with tropical and non-tropical sprue, where these objective symptoms are found with equal frequency, is no proof against the identity of the three diseases, but it is to be interpreted as a difference in the method of reaction on the part of the juvenile and adult organisms respectively.

The extensive bone changes, which can stamp the clinical picture of late detected coeliac disease to so high a degree as to give the impression of an entirely different affection, are secondary changes and not peculiar to idiopathic steatorrhoea.   They can therefore play no part in deciding the question of the identity of coeliac disease and non-tropical sprue.   Other arguments put forward against the identity of coeliac disease and non-tropical sprue on the one side and tropical sprue on the other are the following : Tropical sprue nearly always commences in adult life, is of an infective nature, and is confined to certain areas in the tropics.

It is not correct that tropical sprue nearly always commences in adult life.   In Ashford's series from Porto Rico of 720 cases of tropical sprue there were eighty-seven patients under the age of 10 years, i.e. 12 per cent.   In 18 per cent. the disease had started between the ages of 10 and 20 years. Manson-Bahr (29) states that ' coeliac disease is commonly found in European children brought up in the tropics, especially in India and Malaya.   I am frequently seeing these patients, in whom there is always to be noted a certain lack of bodily and mental development and who are suspected of having sprue.'   He offers no other ground against these children having sprue than the following.   'I am convinced that sprue does not occur in children.' This is a pure postulate which is not based upon any clinically established fundamental difference between the coeliac disease in these children and tropical sprue.   That sprue is an infective disease while coeliac disease and non-tropical sprue are not, is likewise a postulate.   There is no proof to date that tropical sprue is due to an infection.

It is quite easy to understand that physicians who have devoted themselves to tropical diseases get the impression that the particular geographical distribution of these diseases is a deciding factor in regard to the diagnosis. On the other hand, the objection may be raised that wherever the cause or causes of a disease exist or can be present, in such places will the disease be found to occur.   In the past we have been in the habit of believing that beri-beri was a disease with a definite geographical distribution.   Modern

investigation has shown that it is observed wherever the aetiological factor of the disease—avitaminosis B_1—obtains, for example, in Iceland and Newfoundland.   In the same way it has been shown that pellagra is found outside those countries to which it was previously considered to be confined.   The occurrence of non-tropical sprue has been established in Syria, Morocco, Algiers, Constantinople, Italy, Germany, Holland, France, Belgium, Great Britain, Denmark, Norway, and Sweden.   Sprue, then, is not limited to the tropics, but is gradually being displaced from these countries and is being noted more and more frequently towards the North, in exactly the same way as we can observe its appearance in both the Southern and Northern States of America.   This fact is one which specialists in tropical diseases may perhaps find difficult to admit, but it is nevertheless one which has got to be admitted.

Summary

The dominant symptoms of idiopathic steatorrhoea are the metabolic disorders which are entirely identical in the three sub-groups : coeliac disease, non-tropical sprue, and tropical sprue.   The derangement of metabolism is characterized by : 1. An abnormally large quantity of fat excreted in the faeces; 2. A normal, or in some instances a slightly increased nitrogen excretion; 3. A flat blood-sugar curve; 4. A raised rate of basal metabolism.   Of these abnormal manifestations the steatorrhoea is the primary one and is constantly noted in the acute stages of the disease.   In the very earliest stages it may perhaps be less in amount or absent.   In accordance with the experiments described the steatorrhoea is to be regarded as due to a diminished absorption of the fat contained in the food.

The normal, or in some cases slightly raised nitrogen excretion sharply defines idiopathic steatorrhoea from the majority of cases of chronic pancreatic steatorrhoea, where the nitrogen excretion in the faeces may amount to as much as 13–18 grm. per day.

The flat blood-sugar curve is an almost constant phenomena in coeliac disease, is found very frequently in non-tropical sprue and likewise in tropical sprue.   The flat blood-sugar curve disappears very often during the passive stages of the disease, but it may persist.   No objection of any significance has so far been advanced against my view that this flat curve is due to a derangement in the regulation of the blood-sugar.

My experiments in relation to the respiratory quotient have shown that carbohydrates are digested and absorbed in a normal manner.   The frequently noted fermentation of the faeces is not a starch fermentation, but is dependent upon the acidity of the faeces (55, p. 115).

The raised basal metabolism is less constant in its occurrence, but it has been noted in coeliac disease as well as in both non-tropical sprue and tropical sprue.   It is probably due to a functional disorder of certain endocrine

glands.   A lowered rate is not an unusual finding in association with severe emaciation from various causes, and is therefore not a characteristic feature of idiopathic steatorrhoea.

The above mentioned metabolic disturbances are not collectively found occurring together in any other disease than idiopathic steatorrhoea and are therefore pathognomonic of it (see p. 364, footnote).   The positive finding of steatorrhoea in association with a flat blood-sugar curve is usually sufficient ground upon which to base the diagnosis.

The disordered calcium and phosphorus metabolism frequently observed in idiopathic steatorrhoea, with the clinical symptoms consequent to them, are not peculiar to the disease, inasmuch as both changes are found in chronic steatorrhoea of pancreatic origin and in biliary fistula accompanied by steatorrhoea.   The derangement of the calcium and phosphorus metabolism is secondary to the steatorrhoea and conditioned by it mainly through a hypovitaminosis D.   The resulting clinical symptoms are seen most constantly in coeliac disease, as childhood is the most impressionable age for disorders of this nature.   When the disease commences in adult life outside the tropics as non-tropical sprue, these clinical sequlae are less frequent on account of the considerable storage of calcium and phosphorus in the adult osseous system.   The question of their occurrence in tropical sprue has so far been only very little investigated.   The fact that they are less frequently observed in this sub-group may perhaps depend upon the powerful source of vitamin D afforded by the strong sunlight.

With regard to the pathogenesis of the remaining clinical symptoms I must refer to my monograph (55, p. 172).

More recent investigation has furnished the following information: the hyperchromic anaemia observed with equal frequency in both tropical and non-tropical sprue may be explained in certain cases as evidence of hypovitaminosis B occasioned by abnormal fat-contents of the intestines.

The dilatation of the colon often noted in idiopathic steatorrhoea in many instances has its commencement in the sigmoid flexure and descending colon, and is associated with a less pronounced sacculation of the large intestine.   It can probably be explained as a primary atony of the bowel.

The frequently noted symmetrically distributed patches of pigmentation without hyperkeratosis are probably dependent upon hypovitaminosis B.

The typical glossitis of tropical sprue occurs with equal frequency in non-tropical sprue.   For some reason unknown it is seen less often in coeliac disease, but it does occur, and presents the typical appearance.   In certain cases, at any rate, it may probably be regarded as a symptom of hypovitaminosis C or B.

Case Records

Case 1.   Male, farmer, born in 1890.   Reg. No. 256/34.

Family history: negative, no history of rickets or diarrhoea.   Normal development.   From 10 to 14 years of age, constipation alternating with

diarrhoea ; otherwise perfect health until age of 40 years. At this time the patient began to suffer from diarrhoea, with 6–7 bowel movements a day, and tenesmus. The stools were thin, slimy, and bloody.

April 1931 : *Ewald test meal*: 16 c.c.; acidity 16/62. *Haemoglobin* 42 per per cent. *Red-blood count* 3,700,000. *Colour index* 0·7. Treatment with diet and iron. May 1931 : *Haemoglobin* 36 per cent. *Blood-pressure* 135/90. No diarrhoea ; tiredness unchanged. No dyspepsia ; bowel movement only once a day ; stools sometimes a little thin. *Haemoglobin* 31 per cent. *Red-blood count* 3,700,000. *Colour index* 0·5. *White-blood count* 7,000. *Ewald test meal*: 20 c.c.; acidity 0/7. *Weight* 54·5 kg. *Faeces*: no blood. *Urine* normal. *Ewald test meal*: achylia. Treatment ; hydrochloric acid, easily digestible diet, iron, and a liver preparation (corresponding to 200 grm. raw liver, daily).

1932 : *Height* 164 cm. *Weight* 59 kg. *Blood-pressure* 130/85. *Urine* normal. *Haemoglobin* 41 per cent. *Red-blood count* 4,700,000. *Colour index* 0·72. *Neutrophile leucocytes* 74 per cent. ; *eosinophils* 1 per cent. ; *lymphocytes* 20 per cent. ; *monocytes* 5 per cent. *Blood platelets* 690,000. *Ewald test meal*: 24 c.c.; acidity 36/78. *Faeces*: + fat, – mucus – blood. *Roentgenography*: stomach of normal appearance ; no strictures of the intestines ; the transverse colon formed a large loop in the left side of the abdomen ; the descending colon and the sigmoid were large, the sigmoid being in the right side of the abdomen. *Blood-sugar curve*, after ingestion of 70 grm. glucose : low and elongated curve. Fasting blood-sugar 81 mg. per cent. ; maximal blood-sugar 132 mg. per cent. (70 minutes after ingestion of glucose) ; final value 92 mg. per cent. *Serum calcium* 8·7 mg. per cent. *Stools* light in colour, foamy ; not particularly bulky. *Diagnosis*: non-tropical sprue.

July 1933 : *Weight* 61·5 kg. *Blood-pressure* 115/65. *Haemoglobin* 60 per cent. *Red-blood count* 4,800,000. *Colour index* 0·62. *White-blood count* 5,600. *Blood picture* normal. Easily fatigued, occasionally colicky pain in abdomen. No diarrhoea on constipating diet, but the patient was unable to work, as he has diarrhoea at once when he tried to work. During the periods of diarrhoea 5–6 bowel movements a day, sometimes at night too. There had never been any stomatitis, and never tetany, but paraesthesiae and spasms of the lower extremities.

The patient looked fairly healthy, of vigorous build, showed no signs of past rickets. *Height* 164 cm. *Weight* 56·6 kg. Subcutaneous fat scanty ; musculature fairly powerful. The forehead was the site of a symmetrical, brownish-yellow, pigmentation extending down on to both cheeks, rather sharply defined. No hyperkeratosis. Some brownish pigmentation of the skin over the distal interphalangeal joints of all fingers. The finger nails were rather spherical, the tips of the fingers being slightly swollen. Otherwise the extremities appeared normal. The reflexes were normal. All teeth were missing. The tongue was smooth on the tip and along the margins on both sides ; there was no stomatitis or glossitis. Lungs and heart normal. *Abdomen* large (circumference 79 cm.), pronounced tympanites ; Chvostek's and Trousseau's signs absent. *Blood-pressure* : 105/65. *Ewald test meal*: 9 c.c. ; acidity 0/18 ; no retention after 6 hours. *Faeces*: 150–300 grm. per 24 hours ; no blood, no mucus, + fat, catalase value 54. *Urine* normal. *Roentgenography*: stomach and duodenum of normal appearance ; normal passage through the small intestine ; no evidence of osteoporosis in the pelvis, legs, and feet. *Basal metabolism*: 106·5 per cent.

Blood Examination

Date.	Hb. %.	R.B.C. (millions).	C.I.	White B.C.	Reticulocytes.	Volume %.	Volume index.
19.7	68	4·62	0·73	6,800	—	—	—
6.8	74	5·83	0·63	8,280	< 1 %	—	—
2.10	88–91	5·85	0·80	5,600	< 1 %	41·5	0·84

Red-blood count: Normal, except for a moderate degree of anisocytosis. *Average diameter* 8·14 μ; 54 per cent. of the cells less than 8·57 μ. *Blood-sugar curve*, fasting; 99 mg. per cent. after ingestion of 62 grm. glucose: rise from 104 mg. per cent. to 129 mg. per cent., blood taken for this examination every 10 minutes. *Urine*: no sugar. *Blood calcium*: 10·7 mg. per cent.; 8·6 mg. per cent. *Metabolism of fat and protein*, see Table V. *N and Ca balance*, see Tables VII and VIII. *Serum lipoids*, after ingestion of 100 gm. olive oil, see Table VI.

Case 2. Male, banker, born in 1881. Reg. No. 317/33.

Family history: Mother said to have had stomach trouble ('the food did her no good'). Past history: of good health in childhood, except for an attack of jaundice; he developed normally. At the age of 40 years he began to be troubled with diarrhoea after dinner parties.

1921: Protracted attack of diarrhoea, with pale foamy stools. *Ewald test meal* 38 c.c.; acidity 60/82. *Haemoglobin*: 84 per cent. *Weight* 53 kg. *Height* 172 cm. *Faeces*: no blood, light grey in colour. He was treated with pancreon. On discharge from hospital the stools were formed, and he had gained 5 kg. in weight. This improvement lasted but a short time, and diarrhoea recurred.

1924: Tingling and tiredness of the legs, eczema. Considerable tenderness of the muscles of the lower extremities, no disturbance of sensibility, no ataxia; cerebrospinal fluid normal. *Diagnosis*: polyneuritis.

1933: Diarrhoea increasing, appetite good, no stomatitis, very thin, abdomen increased in circumference, voice hoarse, pains and paraesthesiae of the feet and lower extremities, oedema of the ankles, burning of the tongue.

Admitted to the St. Elizabeth Hospital on November 10, 1933.

Marked emaciation and diffuse muscular atrophy; slight arcuate kyphosis of the upper part of the dorsal spine. *Height* 170 cm. *Weight* 50·5 kg. No sign of old rickets, on the forehead areas of brown pigmentation, fingers slightly clubbed, nervous system normal, heart and lungs normal, abdomen large, doughy, and soft, measuring 80 cm. in circumference; no jaundice, mucous membrane slightly anaemic, pulse, 48–52, regular. Chvostek's and Trousseau's signs are negative.

Urine: normal. *Ewald test meal*: 27 c.c.; acidity 55/65; no retention 6 hours after the test meal. *Faeces*: 190–700 grm. in 24 hours, mushy in consistency, light yellow in colour. *Catalase* value: 11. *Wassermann test* negative. *Blood-pressure*: 110/75–96/45. *Blood-sugar curve*; fasting 74 mg. per cent., after ingestion of 52 grm. glucose: rise from 92 mg. per cent. to 115 mg. per cent., samples of blood taken every 10 minutes. *Urine*: no sugar. *Blood Ca*: 8·5 mg. per cent.

Blood examination: serum colour (Meulengracht) 4. *Haemoglobin* 84 per cent. *Red-blood count*: 3,960,000. *Colour index*: 1·06. *White-blood*

corpuscles : 4,100. *Reticulocytes* : < 1 per cent. *Volume percentage* : 35. *Volume index* : 1·03.

Roentgenography : No abnormalities of the pelvis, legs, hands, and forearms : no osteoporosis of either foot ; normal passage of the contrast meal through the small intestine in 8 hours. No stenosis. *Metabolism of fat and protein*, see Table V. *N and Ca balance*, see Tables VII and VIII. *Basal metabolism* (Nov. 20) : 64·7 per cent. and 65·2 per cent. *Serum lipoids*, after ingestion of 100 grm. olive oil, see Table VI.

After his discharge from the hospital the patient felt fairly well for some length of time on a mixed diet *including* a relatively large amount of fruit and vegetables, besides the preparation ' Spinatin ' (vitamins A, B, and C). There were periods of diarrhoea, however, but only brief.

February 1934 : Severe diarrhoea, stools whitish grey, marked debility, and increasing oedema. Lost a great deal of strength, blood urea concentration 168 mg. per cent., went into a condition of uraemic coma and died. Permission for autopsy could not be obtained.

Case 3. Male, farmer, born in 1900.

No tuberculosis in the family. Past history of rickets. He developed as a normal boy, but at the age of 10 years he had an attack of gastritis. The present illness began eight years ago.

1923 : Severe anaemia, stomatitis, and gastric achylia. The stools were said to have been normal.

June 1924 : A severe attack of diarrhoea, with 2–3 bowel movements a day, of gruel-like consistency and whitish in colour, accompanied by colicky pains in the abdomen. He showed at the same time a marked anaemia, and lost altogether 18·5 kg. in weight. He was treated for anaemia. The stools were rather light in colour, copious, and thin. Under treatment in hospital he gained 11·5 kg. in weight, haemoglobin 97 per cent. Since that time he has been under medical treatment, partly at home and six times in hospital. His symptoms have continually been of the same character : attacks of diarrhoea, with copious thin stools several times a day, accompanied by colicky pains in the abdomen, sometimes with vomiting. Marked emaciation during the periods of illness, followed by strikingly rapid gain in weight. Tiredness, good appetite, loss of vigour, anaemia, temperature normal, no ascites or palpable tumour in abdomen. The passage of an opaque meal through the small intestine showed no evidence of stricture.

1927 : *Basal metabolism* 130–131 per cent. *Blood-sugar curve*, after ingestion of 60 grm. glucose, rise from 72 to 101 mg. per cent.—a total rise of 29 mg. per cent., with samples of blood taken every 15 minutes.

1932 : His condition had been getting slowly worse during the past 5 years, periods of diarrhoea, lasting 1–2 months with intervals of 1–2 months, with meteorism and flatulence, 5 or 6 thin copious stools a day, without pain. The faeces were thin and stinking, sometimes foamy. Nausea and frequent attacks of vomiting, loss of weight, and sensations of discomfort over the loins and in the chest. Paraesthesiae of the arms and legs, the muscles stiff, and the hands were clenched in the tetany position, cramps of the calves of the legs. No fever nor night sweats. *Diagnosis* : chronic enteritis ; (defective fat digestion) ; megacolon ; anaemia ; asthenia ; hemeralopia ; tetany. Pluriglandular insufficiency, possibly Addison's disease.

The patient was of average height (166 cm.) and extremely emaciated (weight 4 kg.). No signs of past rickets. His abdomen was large, and the

lower part of the thorax wide. His arms and legs were strikingly thin, with diffuse atrophy of the muscles; the muscle power was slight, and the tonus weak. Skin and mucous membranes not pale. Extensive pigmentation in the face, and also some pigmentation of the arms and legs. In the face there was an area of marked pigmentation of the skin of the forehead, extending quite symmetrically to both sides, from the glabella out towards the temples, besides an area of pigmentation extending across the nose out under both eyes, pigmentation of both cheeks. Pupils normal, both Chvostek's and Trousseau's signs present, hearing and vision were good, but he said he had become night-blind. Fauces, no abnormality; tongue clean, no pigmentation of the mucous membrane of the mouth, no enlargement of lymph glands, spine straight. Blood-pressure 110/75. Abdomen large, dome-shaped, and tympanitic, no palpable abnormality. The extremities were emaciated, the muscle power weak.

The colon took 3 litres of an opaque enema, the sigmoid and descending colon being enormously dilated.

Gastric analysis on seven occasions showed normal acidity. Blood examination showed a slight degree of anaemia (haemoglobin 79 per cent.), perhaps of hyperchromic type.

On microscopic examination the faeces contained neither starch, fat, mucus, nor connective tissue. The fasting blood-sugar value was 88 mg. per cent. The blood-sugar curve after ingestion of 1 grm. glucose per kg. of body-weight (samples of blood taken every 15 minutes) shows a rise from 72 mg. per cent. to 107 mg. per cent., and a fall of 63 mg. per cent. after 3 hours, 68 mg. per cent. after 4 hours, Blood urea: 16 mg. per cent. Urinary diastase: 16. Sedimentation test (1 hour): 16—19—15. The temperature was normal throughout his stay in the hospital, except for an occasional rise to about 38° C.

Blood Examination

Year.	Date.	Hb.	R.B.C. (millions).	C.I.	W.B.C.	Neutrophils.	Eosinophils.	Basophils.	Lymphocytes.	Monocytes.	Serum colour.	Red blood-picture.
1923	28.8	32	4·1	0·4	5,000	83%	—	—	17%	—	—	No abnormalities except for pessary forms.
1923	10.12	57	6·2	0·46	—	—	—	—	—	—	—	—
1924	29·2	87	6·17	0·7	4,960	50%	10	0·5	42·4	5·5	3	Slight anisocytosis, some hyperchromasia; no nucleated cells.

Osmotic resistance (+). Haemolysis at 0·42 % NaCl. Coagulation time 5½ min.

Case 4. Female, born 1898.

No family history of tuberculosis. No past history of rickets. Onset of menses at 14 years; one parturition. From the age of 10–14 years: tendency to thin stools, stopped very easily by bismuth subsalicylate. During the following 16 years her bowel function was perfectly normal; all kinds of food agreed with her until 6 years ago at the age of 30 years, when she began to suffer from her present illness, manifesting itself by 1–2 mushy and very copious stools, greyish-white or whitish-yellow in colour, pungent, and

foamy. As a rule the first defaecation took place at about 5–6 a.m. To begin with, the diarrhoea appeared periodically, lasting about one week, at intervals of about one month, but all of a sudden there might be 10 stools a day, all very thin. The stools were extraordinarily copious, greyish-white in colour, and foamy, fermenting strongly. She had some gripes, but no actual pain; there was, at the same time, a marked emaciation and debilitation. There were no symptoms of dyspepsia, and no signs of stomatitis. She soon noticed, especially in the summer, the appearance of brownish spots and patches on her face, in particular on the forehead and chin. During the bad periods the haemoglobin percentage would, as a rule, fall off to about 60 per cent., but it has always been possible to increase it by treatment with iron.

In the summer of 1934 the patient was under treatment in a hospital for simple anaemia, emaciation, and fatty diarrhoea. At that time the examination showed: *Haemoglobin* 50 per cent. *Red-blood count* 3,900,000. *Colour index* 0·89. *White-blood count* 2,800. *Neutrophils* 46 per cent. Some anisocytosis and poikilocytosis; *Ewald test meal*: acidity 20/55. *Faeces*: no blood. *Wassermann reaction* negative. *Weight* 39 kg., areas of pigmentation on the face, especially along the hair-line. She improved considerably during her stay in hospital; haemoglobin 79 per cent.

1935 : Very emaciated, moderate degree of dorsal kyphosis, pupils normal, slight yellowish pigmentation of the skin over the forehead and more marked pigmentation on both sides of the chin, these areas being symmetrical, sharply defined, extending up on both cheeks. No hyperkeratosis. The tongue was smooth, its tip was red, and there was a swelling of the papillae, extending from the tip to the base of the tongue.

Chest emaciated. No distension of abdomen, circumference 62 cm., extremities very thin.

Urine: normal. *Ewald test meal*: 85 c.c.; acidity 37/62; 0 mucus.

Blood examination, November 29: *Haemoglobin* 80 per cent. *Red-blood count*. 4,350,000. *Colour index* 0·92. *White-blood count* 5,400. *Neutrophils* 68 per cent. *Blood-pressure*: 95/50. *Serum calcium*: 11·05–11·5 mg. per cent, *Basal metabolism*: 107–106·6 per cent. *Glucose tolerance test* (ingestion of 39 grm. glucose): rise of the blood-sugar value from 101 up to 152. *Serum lipoids*, see Table VI. *Metabolism of fat and protein*, see Table V. *N and Ca balance*, see Tables VII and VIII.

Case 5. Female, married, born 1893.
Past history: In childhood and adolescence had cervical adenitis, normal development, menses from the age of 16 years, one normal parturition, 16 years ago. When 18 years old she had to work in a factory; she lived mostly on coffee, bread, and tea, and seldom had meat or vegetables.

At 19 : Large, thin, greyish-yellow stools, 6–7 bowel movements in the morning, pain in the epigastrium, not particularly severe, accompanied by profuse salivation and often by vomiting, weighed only 42 kg. (height 162 cm.), anaemia, tiredness, dizziness, paraesthesiae of the fingers, and fraying of the finger nails, skin dry, scaly, dirty-greyish in colour. Treated with iron and diet, diarrhoea improved, but general condition persisted unchanged for many years. Two years ago: haemoglobin 40 per cent., treated with liver preparations haemoglobin rose to 80 per cent., skin and finger nails again normal.

August 1932: Gradually worse; weight decreased from 54 kg. to 48 kg.;

felt very tired, pain in the epigastrium, followed by vomiting and diarrhoea, very thin, never had attack of cramp, nor stomatitis, no oedema.

December 1932 : Small, slender, well built. *Height* 162 cm. *Weight* 46 kg. No signs of old rickets.

Nervous system : Normal, musculature poorly developed. Scars of tuberculous adenitis on left side of neck, also symmetrical areas of brownish pigmentation extending up over both sides of the lower jaw, no hyperkeratosis. Teeth absent, excepting incisors, tongue almost smooth ; no glossitis. *Heart and lungs* : normal. *Abdomen* : large, distended, circumference 74 cm. ; slight oedema of the legs, pulse 64.

Urine : normal. *Wassermann* : negative. *Blood-pressure* 110/60. *Ewald test meal* : 40 c.c. ; acidity 25/30. No retention after 6 hours. *Faeces* : no blood ; excess fat.

Roentgenography of the stomach and duodenum shows no abnormalities. No stricture of the *colon* ; the sigmoid colon was very long, and so was the transverse colon. Passage through the ileum normal. *Pelvis* : no osteoporosis. *Lungs* : no infiltration.

Blood examination : Haemoglobin 78 per cent. *Red-blood count* 3,400,000. *Colour index* 1·15. *White-blood count* 5,400. *Neutrophils* 60 per cent. No anisocytosis ; no poikilocytosis ; no nucleated red cells. Average diameter 8·34 μ. *Blood calcium,* 10 mg. per cent. *Basal metabolism,* 125·3 per cent. *Respiratory quotient,* 0·81. *Metabolism of fat and protein,* see Table V. *N and Ca balance,* see Tables VII and VIII.

Blood-sugar curve, fasting 6·5 mg. per cent., after ingestion of 50 grm. glucose : rise of the blood-sugar level from 65 mg. per cent. to 90 mg. per cent. ; blood taken every 10 minutes.

The patient was treated with hydrochloric acid, pure diet + 500 c.c. milk. She gained 2 kg. in weight ; the faeces were formed, the bowels moving daily, and the stools of normal colour ; haemoglobin 78 per cent. She was given Exhepar (liver extract), corresponding to 100 grm. of raw liver, three times daily.

Roentgenography shows normal passage of the contrast meal through the small intestine, with good emptying into the large intestine. Thirteen to fourteen hours after intake the contrast meal was demonstrated in the ascending and transverse colon.

September 1933 : Tiredness, repeated vomiting, attacks of diarrhoea (2–3 copious greyish stools daily), no glossitis, thin, pale, circumference of the abdomen 76 cm. *Blood-pressure* 100/50. *Ewald test meal* : 60 + 50 c.c. ; acidity 0/15. No retention after 6 hours. *Faeces* : no blood ; excess fat ; light greyish.

December 1933. *Blood examination* : Haemoglobin 78 per cent. *Red-blood count* 3,870,000. *Colour index* 0·9. *White-blood count* 5,600. *Reticulocytes* 2 per cent. *Neutrophils* 57 per cent.

Red-blood cells : average diameter 8·74 μ. *Serum colour* (Meulengracht) : 2. *Serum calcium* : 10·0 mg. per cent. *Blood-pressure* 90/40. *Blood-sugar, fasting* : 75 mg. per cent. *Blood-sugar curve,* after ingestion of 47 grm. glucose : rise of the blood-sugar level from 75 mg. per cent to 110 mg. per cent. ; blood taken every 10 minutes. *Metabolism of fat and protein,* see Table V. *N and Ca balance,* see Tables VII and VIII. 4th day : 475 grm. faeces contain 59·8 grm. fat and 3·2 grm. N.

Treatment: Bananas + milk, beginning with $\frac{1}{2}$ litre and increasing to 2 litres. The vomiting became less frequent; the pain subsided somewhat; the stools were formed or mushy, but more greyish. Subsequently the patient was given spinach, vegetables, chopped meat, liver paste, bread, eggs, and plenty of fruit of various kinds. At the discharge from the hospital her weight was 49 kg.; the bowel moved once daily, with formed faeces; she had no vomiting; and she was feeling well. She was given Exhepar, corresponding to 200 grm. of raw liver, daily.

Case 6. Male, pharmacist, born 1877.

At 12 years: periods of diarrhoea, developed normally and did well at school. Apart from the attack of diarrhoea at the age of 12 years, he was perfectly well until the age of 27, when he began to have periodic attacks of diarrhoea, with up to 11 stools a day, lasting 3–4 weeks. Often these attacks of diarrhoea were accompanied by aphthous stomatitis. He lost a good deal in weight during these periods, but gained it again rather rapidly when the bowels became normal. These periods of diarrhoea appeared now and then for several years; on the whole, however, he had no intestinal troubles at the age from 35 to 45 years. At the age of 45 years he had again a period of diarrhoea. As a rule all kinds of food agreed with him.

September 1932: Noticed that stools were greyish-white, and very voluminous.

1933: Persistent diarrhoea, flatulence, abdominal pain, tetany, with elevation of the temperature up to 39° C.

Emaciated and rather pale, abdomen large and tympanitic; tenderness on palpation along course of colon. *Wassermann*: negative. *Widal*: negative. *Ewald test meal*: 25 c.c.; acidity 0/34.

Blood examination: *Haeomoglobin* 67 per cent. *Red-blood count* 2,500,000. *Colour index* 1·3. *White-blood count* 2,200. *Neutrophils* 53 per cent. *Serum calcium* 6 mg. per cent. (during attack of tetany); 7·1 mg. per cent.; 9·5 mg. per cent.; 8·2 mg. per cent. *Blood-pressure* 95/55. *Temperature* 39·9° C. in the evening. *Blood-sugar curve*: rise from 95 mg. per cent. to 138 mg. per cent., blood taken every 15 minutes.

June 1933: Extremely emaciated, height 173 cm., weight 52 kg., diffuse muscular atrophy, bones appeared normal, no sign of old rickets, tongue smooth and atrophic, aphthous stomatitis of the same appearance as is typical of sprue. No dyspepsia, heart and lungs normal, abdomen large, measuring 88 cm. in circumference, abdominal wall thin, Chvostek or Trousseau signs negative, no tenderness of the bones.

Urine: normal. *Ewald test meal*, 26/6: 38 c.c.; acidity 25/40; no retention. *Metabolism of fat and protein*, see Table V. *N and Ca balance*, see Tables VII and VIII.

Roentgenography: The pelvis, feet, and legs showed rather pronounced osteoporosis; the hands and fore-arms show no abnormalities.

Opaque enema: Considerable dilatation of the sigmoid, which is very long, and of the descending colon. The transverse and ascending colon showed faint haustration, but no distinct dilatation.

Treatment. On July 1st the examination diet was discontinued and the patient was given, to begin with, about 1,000 grm. strawberries, 500 grm. bananas, and 1·5 litres milk daily. On this diet his temperature subsided to normal within a few days, and his general condition improved

considerably. Then his diet was gradually extended to include bread, eggs, chopped meat, fish, vegetables, besides fruit and milk, so that he was practically on a mixed diet, and he was discharged from the hospital. His weight increased from 50·2 kg. to 57·7 kg. In addition he was given Hepsol (liver preparation) by intramuscular injection, 2 or 3 c.c. daily, from July 4 to July 15. After this he was given Ventriculin (stomach preparation) 20 grm. twice daily. He was also given calcium carbonate and phosphate (1 teaspoonful = 3 grm. twice daily) and Ultranol (15 drops thrice daily); later on, quartz light-baths.

Under this treatment the stomatitis disappeared, but the stools were still greyish in colour and voluminous at the time of his discharge.

He then went to North Italy. On his return home, at Christmas 1933, he weighed 68 kg. (gain of 10 kg.). He felt perfectly well and looked well, but was still troubled with flatulence. Defaecation regular, once daily, the faeces being light brown in colour. A very mixed diet agreed with him, and he kept taking a good deal of fruit and vegetables daily.

Case 7. Male, farmer, born 1898.

Family history: One sister (Case No. 8) suffered from a similar affection to this patient, but in a more pronounced degree. Three brothers were well.

Ever since childhood: subject to periodic attacks of diarrhoea, such periods lasting on an average 2–3 months, with 2–3 stools a day, the stools being sometimes even watery. Stools light yellowish in colour, very copious. In recent years: oppression in epigastrium, tiredness, considerable loss of weight, no nausea or vomiting, no cramps, burning sensation in tongue and mouth, aphthous stomatitis.

November 1933: Fairly good nutrition. Height 172 cm. Weight 62·7 kg. No anaemia or jaundice, pupils normal. The shape of his head was peculiar, with a small face and a large cranium, suggestive of caput quadratum. The palate was high; all the upper teeth and some of the lower teeth were missing; brownish pigmentation on both sides of the neck, extending downwards and around to the nape. Also marked pigmentation of the radial surface of both fore-arms, extending up on the upper arms, symmetrical, with sharply defined borders.

Tongue was almost smooth on tip and along edges, papillae inconspicuous, thorax somewhat wider below than above, circumference of chest at level of nipples in expiration 91 cm. Abdomen: normal shape; abdominal wall lax. Chvostek and Trousseau negative. *Faeces*: greyish-brown, shiny; output of 350–500 grm. a day. *Urine*: normal.

December 1933. *Blood examination*: *Haemoglobin* 56 per cent. *Red-blood count* 5,230,000. *Colour index* 0·53. *Platelets* 420,000. *Volume* 32·25 per cent. *Volume index* 0·72. *Neutrophils* 62 per cent. *Ewald test meal*, 29/11: 25 c.c.; acidity 0·15; excess mucus. No retention after 6 hours. *Blood-pressure* 100/65 mm. *Serum calcium*: 11·8, 12·0, 11·9, 11·5 mg. per cent. *Basal metabolism*: 104·4 per cent.; 101·3 per cent. *Serum lipoids*, see Table VI.

Case 8. Female, born 1909.

Family history: Mother, aged 58, had been troubled for many years with periods of diarrhoea: one brother was patient No. 7 in this communication.

Patient thought she had suffered from her present illness even from infancy. Periodical occurrence of severe diarrhoea, accompanied by a considerable loss

of weight.   Menstruation since the age of 16, but very irregular, scanty, and with long intervals.   Menses absent for the last $1\frac{1}{2}$ years.   She had noticed that she had grown very slowly.

In 1918–19 (at the age of 8–9 years) she was under treatment for omental tuberculosis, dyspepsia, enteritis, and impetigo.   She was at that time very small and thin.   Abdomen large with meteorism, without any palpable tumour and without ascites.   The haemoglobin was 53 per cent.   Wassermann negative.

In the early part of 1931 (at the age of 21) she was treated for a severe degree of anaemia (haemoglobin 30 per cent.; for other data, see Table II), in a provincial hospital where she stayed for three months.   She improved considerably and gained a good deal in weight.

1933 : Stools mostly thin; rather marked jaundice.   Treated with liver extract and Ventriculin, haemoglobin rose from 15 per cent. to 60 per cent., the red-blood count from 900,000 to 4,700,000.   Ewald test meal, see Table I.

November 1933 : The patient, who was aged 24, was the size of a girl of 14 years (height 157 cm.), delicate of frame and rather thin (weight 40 kg.). She had a vigorous growth of light blonde hair on her head, but there was hardly a suggestion of pubic and axillary hairs.   The skin showed brown pigmentation from light-baths.   In addition, there were some areas of pigmentation on the face, a large area on the forehead extending to the temples, rather sharply defined ; further, a similar pigmentation extended across the nose under both eyes, and over both cheeks, being also rather sharply defined ;   there was also a sharply defined area of pigmentation on the upper lip, extending over on to the cheeks, and a less sharply defined pigmentation of the chin.   The patient claimed she had had this pigmentation of the face ' for a good many years ', and that it always became more marked in her bad periods.   There was no marked hyperkeratotis anywhere.

Both lower extremities were the site of several ecchymoses, mostly 2×2 cm. The patient stated that during the last year she had noticed that such spots appeared spontaneously, being at times very large, and that they were never associated with pain.   There was no bleeding from the gums.

She was well built, but there was some genu valgum, most marked on the right side.   The lower opening of the thorax was somewhat wide, and the abdomen rather large (74 cm. in circumference). The intelligence was somewhat childish. The nervous system showed no abnormalities, but the Chvostek sign was said to have been present a few times ; Trousseau sign not present.   The patient stated, however, that at home, during periods of diarrhoea, she had had attacks of tetany with cramps of the extremities and with paraesthesiae.

The tongue was of characteristic appearance.   It was smooth, with a deep furrow in the middle, and pink in colour.   There was a hyperaemic zone extending across the tongue, about 1 cm. from the tip, and a similar zone along the furrow in the middle, with two zones forming a cross and showing small bright-red punctate elevations, that is, papillae.   A similar condition of glossitis was seen along the margin of the tongue and on the tip.   The patient states that she had often had such spells of glossitis, especially in the bad periods. *Mucous membranes* pale.   Slight systolic murmur over base of heart. *Lungs* normal. *Abdominal wall* well developed : no palpable abnormality, no tenderness on palpation or pressure. *Urine* normal. *Temperature* normal. *Blood-pressure* 95/65, 100/60. *Ewald test meal* and *Blood examination*, see Tables I and II.

Roentgenography: The heart and lungs showed no abnormalities. The pelvis, legs, feet, fore-arms, and hands showed a marked degree of osteoporosis. The cranium showed no definite abnormality.

Basal metabolism: 110 per cent. and 119 per cent.   *Serum calcium*: 11·4–11·8 mg. per cent. (in a good period).   *Fasting blood-sugar*: 64–83 mg. per cent.   *Blood-sugar curve* typically low, rising from 83 mg. per cent. to only 93 mg. per cent., blood taken every 10 minutes.

Gastric analysis (*Ewald test meal*): Amount 29 c.c.   Free acid (Congo) 20. Total acidity 45.   Appearance: excess mucus.

December 1933: *Blood examination*: *Haemoglobin* 53 per cent.   *Red-blood count* 3,190,000.   *Colour index* 0·83.   *White-blood count* 4,800.   *Neutrophils* 54 per cent.   *Eosinophils* 1 per cent.   *Lymphocytes* 41 per cent.   *Monocytes* 4 per cent.   *Serum colour* 4–5.   *Platelets* 364,500.   *Red-blood picture*: aniso-poikilocytosis.   *Serum lipoids*, see Table VI.   *Metabolism of fat and protein*, see Table V.   *N and Ca balance*, see Tables VII and VIII.

Case 9.   Female, single, born 1912.
Family history: One sister suffered from idiopathic steatorrhoea (intestinal infantilism) and died at the age of 11 years.
Past history: In childhood the patient was always subject to 'stomach trouble', diarrhoea, and 'rickets'.   She was always small for her age and delicate of frame, feeble, and always pale.   She began school at the age of 8 years, and got along fairly well with her school work, but she remained undersized, looking four years younger than her age.   Her stools were always stinking, foamy, very voluminous, and greyish in colour.   She never had any cramps.   At 16: no larger than a normal child of 10.   Then began to grow more rapidly, especially after the menses had made their appearance, at the age of 19 years.   Since then: 'stomach' got better, although she was still subject to periods of diarrhoea, with copious stools of a light colour.

March 1934: Diarrhoea (3–4 copious stools a day), colicky pain before and after defaecation, no history of dyspepsia, vomiting, or stomatitis.
Height 160 cm., *Weight* 59·4 kg., nutrition fair, pubic and axillary hair scanty, symmetrical areas of pigmentation on both sides of the forehead, rather sharply defined, beginning in front of the ears and extending up over the eyebrows.   No abnormal pigmentation elsewhere on face or body, shape of head normal, palate rather high, teeth good, no sign of past rickets. The bony frame showed normal lines, pupils normal, skin and mucous membranes slightly anaemic, heart and lungs normal, abdomen a little distended, 81 cm. in circumference, soft, without any palpable abnormalities, reflexes normal, Chvostek's and Trousseau's phenomena not present.   *Urine* normal. *Ewald test meal*: 30 + 25 c.c..; acidity 48/89; no mucus.   No retention after 6 hours.

Haemoglobin 65 per cent.   April 21: *Red-blood count* 4,630,000.   *Colour index* 0·77.   *White-blood count* 7,100.   *Volume per cent* 36.   *Volume index* 0·90.   *Blood picture*: some anisocytosis; otherwise normal features.   *Blood calcium*: 8·95 mg. per cent.   *Faeces* copious, yellowish, great excess of fat.

Glucose tolerance test, with ingestion of 58 grm. glucose, blood taken every 15 minutes: rise of the blood-sugar concentration from 106 mg. per cent. to 124 mg. per cent.   *Basal metabolism*: 104·2; 110·5.   *Blood-pressure* 100/65.

Treatment: Raw milk in increasing doses from ¼ litre up to 2 litres daily; subsequently vegetables, fruit, bread, chopped meat, and eggs.   In addition,

the patient was given spinatin (vitamins A, B, and C) and quartz light-baths.

Case 10.   Male, born 1898.
Past history: No gastro-intestinal symptoms in childhood, lived in Java since 22.   At 23, typhoid fever; at 26, amoebic dysentery.

Since December 1932: Relapses of an intestinal disorder, with violent diarrhoea, repeated vomiting, and abdominal pain.   Two weeks later: aphthous stomatitis.

September 1933: Tropical malaria.   October 1933: relapse of amoebic dysentery.

In January 1934: Stools whitish, aphthous stomatitis; haemoglobin 65 per cent.   The diagnosis of sprue was made, and he was treated in a hospital in Batavia with diet and injections of a liver preparation.   He improved somewhat and went home.   After his return home he felt better, although he was still troubled with diarrhoea.   April 1934: looked somewhat pale, complexion diffusely brownish-yellow, tongue normal, no sign of stomatitis, heart and lungs normal.   Pulse 76.   Abdomen slightly distended, 83 cm. in circumference.   *Weight* 62·7 kg.   *Height* 174 cm.   *Urine* normal. *Ewald test meal*, 40 c.c.; acidity 25/52.   *Faeces* copious, greyish-yellow, about 300–750 grm. a day.   *Microscopic examination*: large amounts of fat, no muscle fibres, no starch.   *Glucose tolerance test*, with ingestion of 65 grm. glucose, blood taken every 10 minutes: rise of the blood-sugar concentration from 113 mg. per cent. to 148 mg. per. cent.   *Serum calcium*: 9·7 mg. per cent.   *Blood-pressure*: 110/65.   *Basal metabolism*: 94·1–101·4 per cent.

Blood examination: *Haemoglobin* 74 per cent.   *Red-blood count* 3,340,000. *Colour index* 1·10 per cent.   *White-blood count* 7,300.   *Volume* per cent 32. *Volume index* 1·11.   *Reticulocytes* 15 per cent.   *Differential count*: *Neutrophils* 60 per cent.   *Eosinophils* 2 per cent.

Roentgenography: Both wrists and knee-joints showed no abnormalities. After infusion the *colon* showed no sign of stricture; the sigmoid was very long; both the sigmoid and the descending colon showed dilatation and poorly defined haustration.

Treatment: To begin with, milk diet exclusively; subsequently fruit and vegetables, gradually purée diet and mixed diet.   Gain in weight: 5 kg.
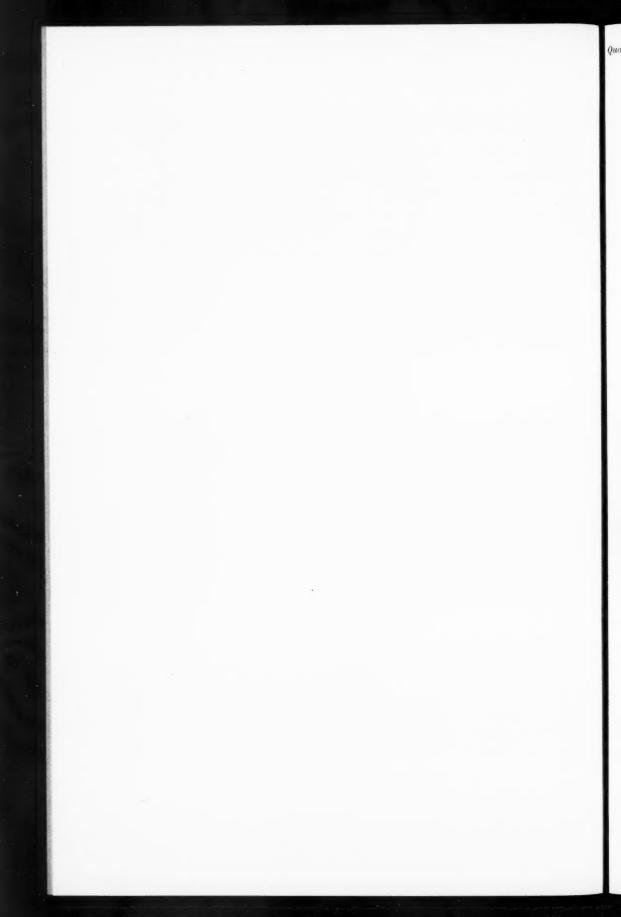
REFERENCES

1. Anderson, A. Greig, and Lyall, A., *Quart. Journ. Med.*, Oxford, 1933, N.S., 2, 339.
2. Bauer, E. L., *Amer. Journ. Dis. Child.*, Chicago, 1928, xxxv. 414.
3. Bennett, I, Hunter, D., and Vaughan, J., *Quart. Journ. Med.*, Oxford., 1932, N.S., 1, 603.
4. Brull, N. L. M., *Bull. d. l'Acad. Roy. de med. de Belgique*, Bruxelles, 1934, 25.
5. Castle, W. B., and Rhoads, C. P., *Trans. Assoc. Amer. Phys.*, Philad., 1932, xlvii. 245.
6. Cathcart, E. P., and Markowitz, I., *Journ. Physiol.*, Lond., 1927, lxiii. 309.
7. Low, C., *Quart. Journ. Med.*, Oxford, 1927, xxi. 753.

8. Colangiuli, A., and Douglas, R. Scotti, *Societa Lombard di Med.*, 1935, iii. 13.
9. Dietrich, H., *Bruns' Beiträge z. klin. Chir.*, Berl., 1925, cxxxiv. 530.
10. Engel, A., *Acta Med. Scand.*, Stockholm, 1931, lxxv. 341.
11. Fairley, H. N., and Kilner, P., *Lancet*, Lond., 1931, ii. 1335.
12. Fanconi, C., *Der intestinal Infantilismus*, Berl., 1928.
13. Findlay, L., and Sharpe, I. S., *Quart. Journ. Med.*, Oxford, 1919–20, xxiii–xxiv. **433**.
14. Froboese, C., and Thoma, E., *Ztschr. f. klin. Med.*, Berl., 1933, cxxiv. 478.
15. Gjørup, E., *Hospitalstidende*, København, 1931, lxxiv, 1205.
16. Haas, S. D., *Journ. Amer. Med. Assoc.*, Chicago, 1932, xcix. 448.
17. Holmes, W., and Starr, P., *Journ. Amer. Med. Assoc.*, Chicago, 1929, xcii. 975.
18. Holst, I. E., *Acta Med. Scand.*, Stockholm, 1926, lxvi. 74.
19. Holst, I. E., *Ztschr. f. klin. Med.*, 1930, cxv. 286.
20. Kassiersky, I. A., *Arch. f. Schiffs- u. Tropen-Hyg.*, Leipz., 1929, xxxiii. 283.
21. Koll, E., *Deutsch. Arch. f. klin. Med.*, Berl., 1931, clxx. 584.
22. Koolemans Beijnen, G. I. W., *Nederl. tijdschr. v. geneesk*, Amsterdam, 1931, lxxv. 5978.
23. Krjukoff, A., *Folia Haemat.*, Leipz., 1927–8, xxxv. 329.
24. Lawaetz and Vogt-Møller, *Hospitalstidende*, København, 1934, lxxvii. 1061.
25. Lehndorff, H., and Mantner, H., *Ergeb. d. inn. Med. u. Kinderheilk.*, Berl., 1927, xxxi. 455.
26. Linder, G. C., and Harris, C. F., *Quart. Journ. Med.*, Oxford, 1929–30, xxiii. 195.
27. Loewy, G., *Presse méd.*, Paris, 1931, lxxxix. 1627.
28. Macrae, O., and Morris, N., *Arch. Dis. Child.*, Lond., 1931, vi. 75.
29. Manson-Bahr, P., *Proc. Roy. Soc. Med.*, Lond., 1933, xxvi. 1054.
30. Manson-Bahr, P., and Willoughby, H., *Quart. Journ. Med.*, Oxf., 1930, xxiii. 411.
31. Marble, S., and Bauer, W., *Arch. Int. Med.*, Chicago, 1931, xlviii. 515.
32. McCrudden, and Fales, H. L., *Journ. Exper. Med.*, Balt., 1913, xvii. 20.
33. McLean, A. B., and Sullivan, B. C., *Amer. Journ. Dis. Child.*, Chicago, 1929, xxxviii. 16.
34. Meulengracht, E., *Acta Med. Scand.*, Stockholm, 1932, lxxviii. 387.
35. Miller, R., *Brit. Journ. Child. Dis.*, Lond., 1923, xx. 88.
36. Moncrieff, A., and Payne, W., *Arch. Dis. Child.*, Lond., 1928, iii. 257.
37. Parson, L. G., *Quart. Journ. Med.*, Oxford, 1927, ii. 1; *Arch. Dis. Child.*, Lond., 1927, ii. 198.
38. Pichard, *Bull. et mém. Soc. méd. hôp. de Paris*, 1933, iii. 389.
39. Roux, J. C., *Arch. des maladies de l'app. digestif*, Paris, xx. 1098.
40. Schaap, L., *ibid.*, 1926, xvi. 914.
41. Schmidt, A. D., *Zentralb. f. inn. Med.*, 1916, xxxvii. 49.
42. Schiødt, *Dansk. med. Selskabs Forhandlinger.*, 1934, 71; *Hospitalstidende*, København, xxxii. 1934.
43. Scott, H. H., *Lancet*, Lond., 1929, ii. 876 and 1135.
44. Seidel, K., *Münch. med. Wchnschr.*, 1910, lvii. 2034.
45. Snapper, *Geneeskundige Gids.*, Gravenhage, 1934, xii. 313.
46. Svensgaard, E., *Acta Paediatrica*, Stockholm, 1929, ix. 22.
47. Tammann, Z., *Bruns' Beiträge z. klin. Chir.*, Berl., 1928, cxlii. 83.
47 a. Tannhauser, S. L., *Münch. med. Wchnschr.*, 1933, viii. 291.
48. Taylor, R., *Trans. Amer. Ped. Soc.*, Chicago, 1922, xxxiv. 100.
49. Thaysen, T. E. Hess, *Acta Med. Scand.*, Stockholm, 1926, lxiv. 292 (343).
50. Thaysen, T. E. Hess, *Verhandl. d. deutsche Gesellsch. f. inn. Med.*, Wiesbaden, 1928, xxiv. 238.
51. Thaysen, T. E. Hess, *Verhandl. d. Gesell. f. Verdauung u. Stofwechlkr.*, Amsterdam, 1928, 151; Leipzig, 1929.
52. Thaysen, T. E. Hess, *Arch. Int. Med.*, Chicago, 1929, xliv. 17–28 and 477–85.

53. Thaysen, T. E. Hess, *Lancet*, Lond., 1929, i. 1086.
54. Thaysen, T. E. Hess, ' Gee's Sygdom ': *Hospitalstidende*, København, 1931, lxxiv. 601.
55. Thaysen, T. E. Hess, *Non-tropical Sprue*, Oxford, 1932.
56. Thaysen, T. E. Hess, *Hospitalstidende*, København, 1933, lxxvi. 325.
57. Thaysen, T. E. Hess, *La Stéatorrhoe idiopathique, Arch. des maladies de l'app. digestif*, Paris, 1934, xxiv. 123.
58. Thorfinn, E., *Acta Med. Scand.*, Stockholm, 1933, lxxx. 389.
59. Vaughan, I. M., and Hunter, D., *Lancet*, Lond., 1932, i. 829.
60. Wintrobe, M. M., and Beebe, T., *Medicine*, Balt., 1933, xii. 187.
61. Vogt-Møller, P., *Relationen mellem B-Vitaminerne og Fødens Indhold af Protein, Fedt og Kulhydrat. Levin og Munksgaard.*, København, 1934.
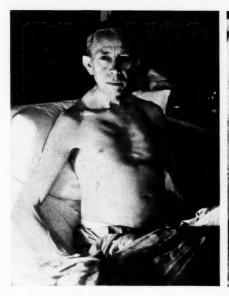
FIG. 1. Case No. 2. Non-tropical sprue

FIG. 2. Case No. 6. Non-tropical sprue
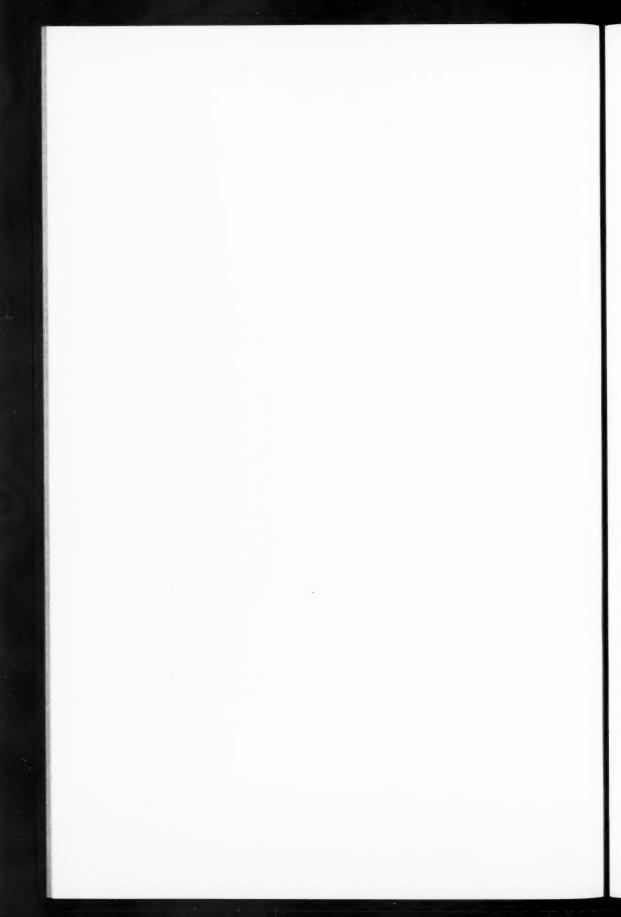
FIG. 3. Case No. 6. Marked muscular atrophy

FIG. 4. Pigmentation of the 3rd phalangue
Case No. 8

FIG. 5. Coeliac disease
Case No. 7

616.24.8

HYPOCHLORHYDRIA IN ASTHMA [1]
WITH SPECIAL REFERENCE TO THE AGE INCIDENCE

By MARJORIE GILLESPIE

(From the Allergy Clinic, King's College Hospital, London)

RECENT investigations have shown that hypochlorhydria occurs more frequently in allergic than in normal people. The term hypochlorhydria includes those cases in which the peak of the free hydrochloric acid curve in a fractional test meal is below 20 units hydrochloric acid.

Hurst (1930) reported hypochlorhydria in 36 per cent. of 66 asthmatic patients of all ages. Bray (1931), using an alcohol meal, found that 80 per cent. of 200 asthmatic children were hypochlorhydric. At Stobhill Hospital, Glasgow, we found 60 per cent. of hypochlorhydrics in a small series of 45 asthmatics of all ages (Adam, 1931). Bray (1934) has summarized the findings of most other observers, from which it would appear that from 40 to 60 per cent. of allergic cases show hypochlorhydria.

It is customary to compare any series of gastric analyses with the normal standards set up by Bennett and Ryle (1921), in which only 15 per cent. were hypochlorhydric. The subjects of that series, however, were all normal students and therefore not strictly comparable with a series varying in age and sex. In a wider group, such as the 1080 New Lodge Clinic cases surveyed by Kohiyar (1926), 36·7 per cent. were found to be hypochlorhydric. Hartfall (1932), also at New Lodge Clinic, found hypochlorhydria in 19 per cent. of 2,448 cases. When compared with these the allergic groups still show a greater proportion of hypochlorhydrics. Bray's series in children is not strictly comparable with the other series quoted, since he used a different meal.

The age incidence of hypochlorhydria is apparently reversed in allergic people. In normal individuals it has been found that low acidity is uncommon in childhood and adolescence but becomes more common towards middle age (Kohiyar 1926, Faber 1927, Hartfall 1932, Bloomfield and Polland 1933). In comparing his series in children with adult series, Bray (1931) noted that hypochlorhydria was found more frequently in allergic children than allergic adults.

The object of the present investigation was to ascertain the age incidence of hypochlorhydria in a series of asthmatics. The analyses reported in this paper were carried out before treatment on unselected new asthmatic

[1] Received June 24, 1935.

patients attending the Allergy Clinic at King's College Hospital. In as many cases as possible the analysis was repeated after about six months' treatment to ascertain any change. The treatment employed in most cases was remedial breathing exercises, the value of which will be reported elsewhere.

Method. Cheney's alcohol test meal, as described by Bray (1931), was used so that results comparable with Bray's results in children might be obtained. The advantages and disadvantages of this method have already been discussed by Bray. By subjecting some of his cases to both methods, he found that in both the highest peak of the curve was practically the same. The alcohol, however, acted as a greater stimulus to acid production in cases of very low acidity. In the present series, 60 c.c. of 7 per cent. alcohol were given to adults and 40 c.c. to children under 10 years. Each sample was filtered, and 2 c.c. used for titration against decinormal sodium hydroxide with thymol blue as indicator (Cole and Adie's method). This has been found to give much more accurate results than those obtained with dimethyl and phenolphthalein (Cole, 1933).

The histamine method (Bloomfield and Polland, 1933); Lander and Maclagan, 1934), so widely used at present, was not adopted for two reasons: first, comparison with Bray's series would no longer be possible, and, secondly, histamine might produce unpleasant general symptoms in asthmatics. It is also a definitely abnormal method of stimulating gastric secretion.

Results. Fractional test meals were carried out on 109 asthmatic patients, of whom 51 were male and 58 female, varying in age from 5 to 67 years.

The results were as follows:

TABLE I

Free Acid Values in 109 Cases

	Cases.	Percentages.
Achlorhydria	17	15·5
Marked hypochlorhydria (below 10 units free HCl)	15	13·8
Slight hypochlorhydria (below 20 units free HCl)	24	22·2
Normal (20–30 units free HCl)	18	16·5
High normal (30–50 units free HCl)	16	14·6
Hyperchlorhydria	19	17·4
	109	100

In about half the series, therefore (51·5 per cent.), the highest point of the curve did not reach 20 units of free hydrochloric acid. Mucus was present in excess in the fasting juice in most of the cases showing hypochlorhydria. It was present in great excess throughout the meal in 22 cases, 19 of which were hypochlorhydric. This would suggest that in some instances the low free acid values obtained might be due to the excess mucus.

The combined acid, which is generally given as about 10 units of decinormal hydrochloric acid, was found to be over 15 units in 55 of the cases. As only 29 of these were hypochlorhydric, an increase in the combined acid

would appear to be as common in cases of normal or high acidity as in those of low acidity.

Since this high combined acidity has not been noted by other observers it might be suggested that it was due to the use of thymol blue as indicator.

Cole has shown that by treating undigested saliva mucin with hydrochloric acid, adding thymol blue, and allowing the mixture to stand, the colour of the thymol blue fades and the free acid content drops to about half its value. He has suggested that this is due to the affinity of one form of the indicator for mucin. In the present series filtration of each sample prevented any interaction between the thymol blue and undigested mucus if present. No difference in the free or combined acid results was found whether the thymol blue was added immediately before or some time before titration. In one case, tested both with thymol blue and phenolphthalein, the combined acid was found to have the same value with both indicators.

In an attempt to elucidate this problem of the importance of mucus, in cases showing a high combined acid figure, the total acidity (i.e. the free + the combined acid) might be taken as a more accurate indication of the acidity of the gastric juice. Hypochlorhydria would then be diagnosed where the total acidity did not reach 30 units of hydrochloric acid after the alcohol meal. The total acidity of the fasting juice was not considered, as it might contain organic acids, such as lactic acid, and so give false readings.

The total acid figures were as follows:

TABLE II

Total Acid Values in 109 Cases

Total acid.			Cases.	Percentages.
None			4	3·7
Below 10 units HCl			10	9·1
,, 20	,,	,,	11	10·1
20–30	,,	,,	20	18·3
30–40	,,	,,	22	20·1
40–60	,,	,,	23	21·1
Over 60	,,	,,	19	17·4
			109	99·8

From these figures 41·2 per cent. of cases showed a low *total* acidity, whereas 51·5 per cent. of the same cases showed a low *free* acidity. It would appear, therefore, that although in 10 per cent. of cases there is a false hypochlorhydria, presumably due to the buffering action of mucus, in the majority there is a definite hyposecretion of acid.

Age groups. When the cases showing low free acidity were separated into age groups the following figures were obtained:

TABLE III

Age Incidence of Cases Showing Low Free Acidity

Age in years.	No. of cases.	No. of cases showing low free acidity.	Percentage of cases showing low free acidity.
1–10	9	8	88
11–15	10	6	60
16–20	7	1	14
21–30	24	10	41
31–40	18	12	66
41–50	24	10	41
over 50	17	9	53

Although the series is not large, these figures tend to show a decrease in the incidence of low free acidity after puberty: 73·7 per cent. of cases under 15 years of age were hypo-acid, whereas between 15 and 30 years only 35·5 per cent. were hypo-acid. Bray (1931) found that low free acidity was more common in children under 10 years of age than in those nearing puberty. He suggested that this decreased incidence of hypo-acidity might be related to spontaneous cures at puberty. The increase between 30 and 40 years shown above may bear some relation to the increased incidence of bronchitic asthma in middle age. This increase will also be partially due to the normal increase in hypochlorhydria with age.

If the *total* acidity is considered in age groups, the great difference in percentage before and after puberty shown by the *free* acid figures is somewhat decreased. Up to 15 years of age low total acidity was present in 55 per cent. (compared with 73·7 per cent. showing low *free* acidity) and from 15 to 30 years of age in 35·5 per cent. of the cases (i.e. identical with the figure of low *free* acidity). The age incidence of both low *free* acid and low *total* acidity are plotted in Graph I.

From these findings it would appear that the asthmatic child tends to overcome the original defect in its gastric juice towards puberty. In the cases under discussion this is borne out by comparing the age at onset of the asthma with the hypochlorhydria found in the present analyses.
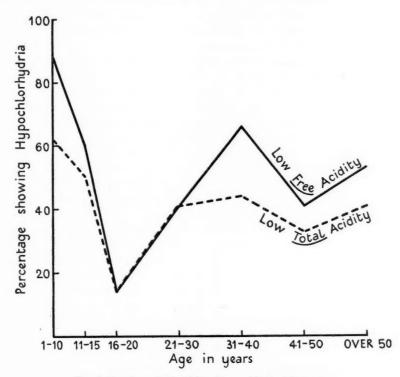
The figures for the age at onset of asthma, given in percentages, correspond fairly closely with those given by Bray (1934) for the age at onset in 4,317 cases of asthma.

TABLE IV

Cases now Showing Low Free Acidity Compared with the Age at Onset of the Asthma

Age at onset of asthma.	No. of cases.	Percentage 109 cases.	Percentage (Bray) 4,317 cases.	No. showing low free acidity.	Percentage.
1–10 years	35	32·0	33·7	19	54
11–20 ,,	17	15·5	14·1	8	47
21–30 ,,	18	16·5	17·5	8	44
31–40 ,,	19	17·4	16·3	11	58
41–50 ,,	15	13·7	10·5	8	53
over 50 ,,	5	4·6	7·9	2	40

It is apparent from the above figures that, taking Bray's figures of 80 per cent. hypochlorhydria in children as correct, a percentage of cases who must have shown hypochlorhydria in childhood no longer do so. This is all the more evident when the nine children now under 10 years are removed from the group. It is then found that of the 26 cases over puberty, in which the asthma began in childhood, only 11, or 42 per cent., now show hypo-acidity.

Graph showing relationship of hypochlorhydria to age.

Sex. Hypochlorhydria occurred in 39 per cent. of 51 males and 62 per cent. of 58 females. This higher incidence in females held true for all ages after puberty. [Hartfall (1932), found that the incidence of achlorhydria increased with age much more in women than in men.] Before puberty both sexes showed about the same percentage of hypochlorhydria. (Bray states that ' the acid curve does not appear to rise towards puberty in girls with nearly the same frequency as in boys '. In view of this it is of interest to note that of the 11 cases over puberty whose asthma began in childhood and who now show low acidity, 9 were females.)

Skin sensitivity. Positive skin tests were found in 56·8 per cent. of 109 cases. Of the 56 cases of hypochlorhydria 32 (57 per cent.) gave positive

skin reactions to one or more proteins. Of the 53 cases with normal or hyperacid curves 30 (56·6 per cent.) gave positive skin reactions.

Second test meals. Test meals were repeated in 52 cases after about six months' treatment: 46 were treated with remedial breathing exercises, and 6 (originally achlorhydric) with dilute hydrochloric acid as advocated by Bray. Acid therapy was stopped for at least a fortnight before the second test.

Of the six achlorhydrics treated with hydrochloric acid, only one, a boy of 10 years of age, showed any improvement at the second test, free acid being present to a height of 6 units; he also showed marked clinical improvement, whilst the others showed none.

In the 46 cases treated with breathing exercises, the following changes were found at the second test:

TABLE V

Comparison of Results of First and Second Test Meals

Results of first test meal.	No. of cases.	Cases showing definite increase in acid.	No. showing clinical improvement.	Cases showing no marked change.	No. showing clinical improvement.	Cases showing decrease in acid.	No. showing clinical improvement.
Achlorhydria	5	2	2	3	0	0	0
Below 10 units	9	5	5	2	1	2	0
10–20 ,,	12	7	7	3	1	2	0
20–30 ,,	7	2	1	3	0	2	1
30–50 ,,	5	0	0	2	2	3	2
Over 50 ,,	8	0	0	6	5	2	2
	46	16	15	19	9	11	5

It will be seen from the above table that the change in the analyses at the second test is considerable. Only 41 per cent. have remained approximately the same. At the first test meal 56·6 per cent. were hypochlorhydric, 26 per cent. were normal, and 17·4 per cent. were hyperchlorhydric. At the second test meal 39·1 per cent. were low, 43·5 per cent. were normal, and 17·4 per cent. were high.

On the whole these figures show a tendency for the low free acid curves to improve after treatment. Since the amount of combined acid was found to be about the same in each case at the second analysis and the total acidity was improved, this would appear to be a true increase in acid. Clinical improvement apparently also coincided with this improvement in gastric acidity.

Discussion

The relation between hypochlorhydria and allergy has been discussed by many workers but no satisfactory conclusion has been reached. It would

appear, however, that the general tendency is to regard the hypochlorhydria as due to a primary defect in acid secretion.

In support of the hypothesis that the low acidity is primary, the age incidence of hypochlorhydria, in the present cases, runs parallel with the age incidence of the onset of asthma, and the highest point in each curve is in childhood. Again, the fact that there is low *total* acid in 41 per cent. of cases would also indicate a primary defect. On the other hand, it might be argued that the excess of mucus, which is slightly alkaline in reaction, had neutralized some of the acid. In cases of high acidity mucus might thus be present in a neutralized and combined form not visible to the naked eye. This excess of mucus has generally been taken to indicate a low form of chronic gastritis. As Bray has pointed out, although probable in middle age, this is unlikely to be the reason for its presence in young children. Might it not be part of a mucous diathesis linked up with allergy and most marked in childhood, since hyperactivity of all the mucous membranes is common in the allergic individual? Hurst (1930, 1934) has instanced the possible mechanical effect of mucus blocking the acid ducts and so producing hyposecretion. He has also suggested that in the present series the excess of mucus might be due to the use of alcohol, since alcohol is an irritant (*Private communication*). Against this view must be put the fact that the mucus was found in greater excess in the fasting juice before the alcohol was given.

From the point of view of nervous control, secretion of acid and inhibition of mucus have been brought about by vagal stimulation in dogs, whilst injection of atropine and of acetylcholine have produced the opposite effect of inhibiting the acid and increasing the secretion of mucus (Loeper and Fau, 1933). The hyposecretion of acid and increased secretion of mucus might then be related entirely to an upset of the normal nervous control. It is impossible, at present, to give more than tentative suggestions as to the causation of hypochlorhydria in asthma. Excessive secretion of gastric mucus would appear to be a factor in its production in the present analyses.

In this series the allergic state, as evidenced by the response to skin tests, does not appear to bear any relation to the hypochlorhydria. Bray (1931) stated that ' a definite relationship does exist between the state of hypochlorhydria and the degree of sensitivity evidenced '. It might be concluded in the present series, that the absence of any relationship between the two is due to the fact that, although in some patients the gastric acidity may increase at puberty, the skin sensitivity acquired in childhood, being due to a more complicated change, persists unaltered.

As evidenced by the second test meals, the gastric acidity in asthma is by no means constant. It is difficult to decide whether clinical improvement produces an increase in acid or an increase in acid promotes clinical improvement. In favour of the latter view, improved digestion of protein would follow increase in acid, and thus one contributory cause in the

production of the asthmatic attack, in some of the patients, would be removed. It is interesting to speculate how far non-specific therapy, such as breathing exercises, might stimulate the production of acid.

A suggestion for future investigation of gastric acidity in asthma would be the repetition of test meals with the estimation of mucus from time to time in asthmatic children, from an early age until after puberty, and the correlation of the results with clinical change.

Summary

1. Fractional test meals were carried out on 109 asthmatic patients. Low free acidity was found in 51·5 per cent. and low total acid in 41·2 per per cent. of cases. Excess mucus and increased combined acidity were also present in many cases.

2. Hypochlorhydria was found to be most common in asthmatic children under 15, and less so in young adults: it again became more common in those nearing middle age.

3. It would appear that gastric acidity does not remain the same throughout life in allergic individuals, but tends to increase in a certain percentage of cases about puberty.

4. Female asthmatics from 15 years of age upwards showed a higher percentage of hypochlorhydria than males of the same age. Before 15 years of age there was practically no difference in the sex incidence.

5. Sensitivity, as shown by skin tests, bore no apparent relationship to the hypochlorhydria.

6. Repetition of the analyses after treatment showed definite change in 59 per cent. of cases. Improvement in gastric acidity in originally hypochlorhydric cases coincided with clinical improvement.

7. The probable factors in the causation of hypochlorhydria have been discussed.

REFERENCES

Adam, J., *Glasgow Med. Journ.*, 1931, cxvi. 81.

Bennett, T. I., and Ryle, J. A., *Guy's Hosp. Rep.*, Lond., 1921, lxxi. 286.

Bloomfield, A. L., and Polland, W. S., *Gastric Anacidity*, N. York, 1933.

Bray, G. W., *Quart. Journ. Med.*, Oxford, 1931, xxiv. 181.

Bray, G. W., *Recent Advances in Allergy*, Lond., 1934.

Cheney, G., *Amer. Journ. Med. Sci.*, Philad., 1929, N.S. clxxxvii, 110.

Cole, S. W., *Practical Physiological Chemistry*, Camb., 1933.

Faber, K., *Lancet*, Lond., 1927, ii. 901.

Fogelson, S. J., *Journ. Amer. Med. Assoc.*, Chicago, 1931, xcvi. 673.

Hartfall, S., *Guy's Hosp. Rep.*, Lond., 1932, lxxxii. 13.

Hurst, A. F., *Report of Asthma Research Clinic*, *Guy's Hosp. Rep.*, Lond., 1930, lxxx.

Hurst, A. F., *Brit. Med. Journ.*, Lond., 1934, ii. 665.

Kohiyar, A. J., *Guy's Hosp. Rep.*, Lond., 1926, lxxvi. 65.

Lander, F. P. L., and Maclagan, N. F., *Lancet*, Lond., 1934, ii. 1210.

Loeper, M., and Fau, R., *Compt. rend. de la Soc. de biol.*, Paris, 1933, cxiii. 981.

Bl

th
an

7·3
fin
ele
ex
Ba
dr
Af
lov
of
1·6

dy
au
in
ar
an
sh
ex
af

ga
se
de
lov
ot
dy

[9

BLOOD pH AND LACTIC ACID IN DIFFERENT TYPES OF HEART DISEASE [1]

By I. HARRIS, E. WYN JONES, AND C. N. ALDRED

(From the Liverpool Heart Hospital)

In this paper are recorded pH, lactic acid, and alkali reserve values of the blood in different types of heart disease, both under resting conditions and after a standard exercise.

Normal pH values for blood are given by Shock and Hastings (1) to be 7·35 to 7·45 for men and 7·35 to 7·47 for women, which agrees with the findings of most authors. Earle and Cullen (2), with the quinhydrone electrode, give as the normal pH value predominately 7·4 to 7·5. After exercise the pH becomes lower. In a well-known experiment on himself Barcroft found that after an ascent of a mountain his CO_2 alveolar tension dropped from 40 mm. Hg. at rest to 35 mm. and the pH from 7·29 to 7·09. After exercise, according to Barr, Himwich, and Green (3) the pH is lowered both in the arterial as well as in the venous blood, and the degree of the decrease stands in definite relation to the amount of work done. 1·020 kg. of work lowers the pH by 0·02, and 4·530 kg. lowers it by 0·04.

Lewis, Ryffel, Wolf, Cotton, and Barcroft (4) came to the conclusion that dyspnoea in certain types of heart disease is caused by an acidosis. These authors found an increase of blood lactic acid in some of the cases they investigated. However, Fraser, Ross, and Dreyer (5) have shown that the arterial blood in such cases is actually more alkaline than normal. Meakins and Davies (6) investigated the carbon-dioxide combining power in cases showing different degrees of heart failure; they found that, apart from extreme cases, CO_2 combining power is normal in this type of cardiac affection. Campbell and Poulton (7) arrived at a similar conclusion.

Closely interrelated with the subject of this paper is the problem of gaseous exchange in heart disease. So far as oxygen is concerned, the consensus of opinion is that only in pulmonary congestion or oedema is oxygen desaturation found in arterial blood (8). The CO_2 content of the blood is low in heart disease, with certain exceptions, according to Porges (9) and others. Fraser, Harris, Hilton, and Linder (10) concluded that in cardiac dyspnoea the blood CO_2 content may be high, low, or normal.

Hill, Long, and Lupton (11), with the Clausen technique, give 10 to 25 mg.

---

[1] Received June 15, 1935.

per cent. of lactic acid in the blood as normal values. Jervell (12) found 20 to 30 mg. of lactic acid in normal individuals, and he also found an increase of lactic acid in the blood of people suffering from heart disease. It is well known that lactic acid is increased in the blood of healthy subjects after severe and moderately severe exercise. Hill (11) found after eighty minutes of work which required an oxygen consumption of 2,260 c.c. per minute, the lactic acid increased from 20 mg. at rest to 58 mg. Owles (13), however, found practically no increase of lactic acid in the blood of the basilic vein after walking exercise of thirty minutes at the rate of over four miles per hour.

Determination of pH. 1. The glass electrode was employed and was adapted for use with blood. As is generally recognized, it is superior not only to the colorimetric but also to other electrometric methods. There are two main difficulties in these determinations so far as biological fluids are concerned. It is not desirable to use paraffin for the purpose of avoiding CO_2 loss, since the contact of paraffin with the glass membrane fouls the electrode. The other difficulty is that of temperature. If determination is made at room temperature a correction factor has to be used which is variously given by different authors. To avoid this difficulty the whole investigation was made in a room heated to body temperature. In addition, it is essential, for various reasons, to make determinations in the shortest possible time. In such circumstances it is important to be sure that a proper equilibrium between fluid and buffer solution has been established. To avoid CO_2 loss the method used was as follows:

Blood was withdrawn from an antecubital vein, as far as possible without stasis, by means of a wide-bore needle to which was attached 6 in. of narrow rubber tubing. About 2 in. from the end of the tubing attached to the needle there was fitted a rubber cap which, when in position, accurately fitted the opening in the electrode rendering it air-tight. Before it was placed in position, however, blood was allowed to flow through the needle and tubing, so displacing any air that might be contained in the lumen. With the needle still in the vein the free end of the tubing was then inserted into the inner chamber of the glass electrode and the rubber cap was fitted closely over the opening. In this position the open end of the tubing lay at the bottom of the inner chamber immediately over the glass membrane and the inner chamber filled up with blood. The lower end of the tubing was covered when only 1 or 2 c.c. of blood had entered the glass electrode, so that only the first 1 or 2 c.c. of blood that entered the electrode vessel came into contact with air. The electrode vessel filled up to the top and overflowed. Meanwhile the electrode vessel continued to fill from the bottom and the blood entering it at no time came into contact with air, even momentarily.

With regard to the cerebrospinal fluid determination, the ordinary cannula in use for this type of work was employed. Connected to it was a piece of fine rubber tubing of a narrow bore, about 3 in. in length. The distal end

of the tubing was inserted in the inner chamber of the electrode as before. A detailed account of this method will be found in the *Journal of Physiology* (1934, vol. 81, p. 197). For the blister fluid, however, we were compelled to use paraffin owing to the difficulties inherent with its collection, but only a very thin line of paraffin was used.

2. The *estimation of lactic acid* in blood and fluid was carried out by the iodometric method introduced by Clausen and modified by Friedemann, Cotonio, and Shaffer, and later by Friedemann and Kendall. The principle of the method is the formation of acetaldehyde from lactic acid when the latter is oxidized by heating with potassium permanganate. The aldehyde is collected, by a process of aeration, into sodium bisulphite solution, and titrated by Clausen's method.

The protein was removed from the blood by the Folin-Wu method, while sugar and other interfering substances were precipitated by means of the Van Slyke copper-lime treatment. In the case of spinal fluid, protein precipitation was carried out according to the modification of the Folin-Wu technique suggested by Beaumont and Dodds, while the sugar was dealt with as in the case of blood. Application of the old and new protein precipitation methods to spinal fluid showed no significant difference as far as the lactic acid content is concerned.

All the estimations were commenced almost immediately after the removal of the blood or fluid, so as to ensure that no extra lactic acid was formed by glycolysis. Double estimations were carried out on nearly every specimen of blood and fluid.

Method employed for ascertaining the venous pressure. The method was that used by Moritz and V. Tabora, and by a number of other observers. A very large needle, larger than the usual serum needle, with a very wide bore, was put into the basilic vein and connected with a manometer containing a solution of 0·7 per cent. of salt and 0·5 per cent. of pot. citrate. The patient lay on a table in the recumbent position; the left arm was put in such a position that the basilic vein was on the same level as the anterior axillary line, the base of the manometer being likewise on the same level. It is essential to take some precaution in regard to coagulation of the blood in the needle. Coagulation may take place at an early stage of observation, in which case the correct reading would be interfered with. To prevent this error it is desirable from time to time to apply pressure to the veins in order to ascertain whether such pressure produces a rise in the manometer.

Relation of pH to lactic acid. In considering the relationship of the two values to each other, the following two factors must be taken into account. In order to counteract a disturbance in the acid base equilibrium an increase in blood lactic acid results in the lowering of the CO_2 tension. But as Hill and his co-workers have shown, the amount of CO_2 driven out after a standard exercise does not correspond quantitatively to the rise of the blood lactic acid level. It is less. Therefore the pH must become lower

whenever large quantities of lactic acid accumulate in the blood-stream. The other factor is as follows:

Lactic acid is produced by the active muscle, and it may become re-absorbed by a muscle in a condition of rest. Walking and climbing stairs may result in a pronounced increase of blood lactic acid in a specimen derived from the veins of the active muscle. But the blood in the basilic vein might not show an equally pronounced hyperlacticaemia. In order to correlate the pH to lactic acid values the nature of the blood-supply of the respiratory centre which regulates the acid base equilibrium must be taken into account.

Now it may be taken for granted that when the patient is at rest an equilibrium exists between pH and lactic acid in all parts of the circulation. Soon after a standard exercise which entails activity of the leg muscles the matter is different. Large quantities of lactic acid will accumulate in the veins of the lower extremities. The arterial blood will contain less lactic acid, and the venous blood in the resting arm least of all. This is in accordance with the findings of Barr, Himwich, and Green (3), whose published tables show that the lactic acid content of the basilic vein was less than that of the arterial blood in leg exercise, and higher in arm exercise. In spite of these theoretical conditions it follows from the tables published by these authors that the lactic acid content of venous blood of the resting arm after exercise shows in the great majority of cases very little difference from the arterial blood, and Eggelton and Evans (14), who, on the whole, confirm the findings of Barr, Himwich, and Green, come to the conclusion that, on the whole, there is no great difference in the amount of lactic acid between the arterial and venous plasma taken from the resting limb, although there are individual variations.

Procedure. All determinations were done on in-patients at the Liverpool Heart Hospital. The patient was wheeled to the lift and taken down to the basement and placed on a couch in a room heated to a temperature of 37° C. No other exertion was involved in the procedure apart from walking, supported, two or three yards on level ground. A specimen of blood was taken from the median basilic vein. All determinations were made from blood taken at the same time. Those who performed the standard exercise walked up and down a flight of stairs for four minutes. All types of cases suffering from heart disease have been investigated, some in a condition of extreme heart failure; in others there was hardly any disturbance of the cardiac function noticeable.

Results

Lactic acid, pH, and alkali reserve under resting conditions. Table I gives determinations of pH and lactic acid in normal cases at rest as well as after the standard exercise employed in this investigation. The margin of error in our method of pH determination is about 0·02—certainly not more than

TABLE I

		pH.	Lactic acid.
H. H.	Before exercise	7·45	23·4
	After ,,	7·47	23·7
I. H.	Before exercise	7·41	21·7
	After ,,	7·41	20·6
N. B.	Before exercise	7·45	23·2
	After ,,	7·42	21·7
N. W.	Before exercise	7·46	15·8
	After ,,	7·46	16·7

TABLE II

pH, Lactic Acid, &c.

	Name.	pH.	Alkali reserve.	Lactic acid.	V. P.	Disease.
1	Morley	7·36	48	44·6	9·0	Congestive failure
2	Keenaghan	7·42	50	37·0	6·5	,,
3	Houghton	7·42	55	31·5	11·0	Chronic myocarditis
4	Magee	7·39	53	30·5	8·5	Hypertony
5	O'Kane	7·47	59	33·0	6·5	,,
6	McMerryman	7·45	55	37·0	5·5	Valvular disease
7	Dunwoody	7·43	52	38·8	9·5	Congestive failure
8	Maclusky	7·40	54	25·6	9·5	Aortic regurgitation and cardiac asthma
9	Sherlock	7·48	62	27·5	7·5	Hypertony
10	Labone	7·43	57	46·0	12·0	Congestive failure
11	Ginnis	7·46	56	46·4	8·0	,, ,,
12	Gillman	7·47	67	28·0	9·0	,, ,,
13	Hannakin	7·44	53	44·5	7·5	,, ,,
14	A. Jones	7·45	60	37·0	12·0	D.H.A.
15	Drewary	7·43	65	39·0	6·5	Cardiac insufficiency
16	Skedmore	7·42	54	36·0	14·0	,, ,,
17	Roberts	7·45	50	48·0	6·5	Congestive failure
18	Stretch	7·46	59	25·0	—	Hypertony
19	Miller	7·41	55	24·0	4·0	Aortic regurgitation
20	Cohen	7·42	52	30·0	10·5	Arteriosclerosis
21	Remington	7·43	60	43·0	8·25	Hypertony
22	Hamilton	7·42	59	33·5	5·5	,,
23	Foley	7·45	53	53·0	12·5	Hyperthyroidism and auricular fibrillation
24	Blower	7·39	50	37·0	—	Myocardial damage
25	Harris	7·45	55	43·0	8·5	Congestive failure
26	Fowler	7·45	53	20·0	9·75	Irritable heart
27	Costello	7·36	49	33·0	6·0	Valvular disease
28	Cheetham	7·45	55	33·0	5·5	Angina of effort
29	Smith (Miss)	7·42	59	34·0	6·0	Auricular fibrillation
30	Dowley	7·39	62	26·0	6·25	Angina of effort
31	Fletcher	7·44	—	35·5	—	Valvular disease
32	Coulton	7·46	—	39·0	—	Hypertension
33	Arrowsmith	7·42	—	31·5	—	Mitral stenosis and auricular fibrillation
34	Callaghan	7·43	—	26·0	—	Hypertension and fibrillation
35	Flynn	7·40	—	35·0	—	Angina pectoris
36	Sanderson	7·42	—	33·0	—	Valvular disease
37	Strenaitis	7·43	—	47·5	—	Congestive heart failure
38	Molyneux	7·33	—	71·0	—	Pronounced cardiac failure and general oedema
39	Woodward	7·45	—	52·0	—	Heart failure

0·03. For lactic acid the margin of error is about 5 per cent. plus or minus. It will be seen that the pH and lactic acid values in normal resting individuals fall within the ranges of values found by other investigators.

In the majority of the patients (Table II) the lactic acid content is above the normal limit of 30 mg. The highest value is shown in Case 38, a case of pronounced heart failure with oedema, who died some weeks after the determination was made. In this instance the pH was 7·33, the lowest in our series, and the lactic acid content was 70·1 mg. Out of 39 cases from this Table, 29 show actually an abnormal increase of lactic acid. These were to a great extent unselected cases from the wards. On the other hand, Table III is made up of 18 cases who clinically exhibited less pronounced evidence of heart failure, so that they were deemed to be suitable for standard exercise. In this series only 8 cases exceeded 30 mg. of lactic acid, and the highest lactic acid value was only 40. It is clear that the average heart patient who is an inmate of a hospital shows an abnormally high blood lactic acid content. On the other hand, all pH values with the solitary exception of Case 38 which showed a lactic acid content of 71, give readings within normal limits. This series includes cases of cardiac asthma. All attempts to correlate clinical evidence such as dyspnoea to pH values failed. These facts become more evident if our material is divided into the following three groups: (1) Cases of congestive heart failure; (2) Cases of hypertension; and (3) Miscellaneous cases. In the first group of cases the average lactic acid level amounts to 40·5, whilst in Group 2 the average lactic acid is 32. Somewhat similar figures are given by Group 3.

In correlation with the degree of heart failure the average venous pressure in Group I is 9 inches of water, whilst it is only 7·35 in the second group. The alkali reserve too, as was to be expected, is lower in the first in comparison to the second group (54·3 first, against 57 in the second, and 56 in the third). Figures for the average pH, however, remain the same in all the three groups. All cases where the blood lactic acid reaches a level in the neighbourhood of 40 mg. per cent. show evidence of pronounced heart failure, and the great majority exhibit some form of oedema; and all these cases exhibit other evidence, such as electrocardiographic, of a damaged heart-muscle. The relation is between lactic acid and the degree of heart failure. Case 13 is instructive in this respect: a case of auricular fibrillation. Lactic acid was determined when he was not under the influence of digitalis. It was 44·5 mg. After the administration of digitalis the lactic acid content sank to 20 mg.

On the whole there seems to be a relation between lactic acid content and alkali reserve. Where lactic acid is low the alkali reserve is high, and vice versa. It has been stated that in cases where lactic acid increases as a result of exertion, CO_2 is driven out of the blood, but that the CO_2 loss does not compensate for the increase in the blood lactic acid content. In such cases the pH is lowered as the result of exercise. In this series of cases under resting conditions, as long as the lactic acid level is not unduly high,

pH values remain within normal limits. Evidently the low CO_2 content which is found in many cases of heart disease compensates fully the lactic acid increase. (It is possible, however, that in Case 38, which has given the lowest reading of pH in our series, the blood CO_2 might have been higher than normal.) In such cases evidently 'a steady state' is reached in lactic acid formation and disappearance on an abnormally high level. Exceptions

TABLE III

pH, Lactic Acid, &c. After Exercise

	Name.	Exercise.	pH.	Lactic acid.	Alkali reserve.
1	Milner	Before	7·42	30	—
		After	7·44	35	—
2	Flynn	Before	7·41	28	—
		After	7·32	28	—
3	Foyle	Before	7·41	40	63
		After	7·31	47	61
4	Fitzsimmons	Before	7·37	26	—
		After	7·32	29	—
5	Smith (Arthur)	Before	7·32	29·5	—
		After	7·26	37.5	—
6	Roberts	Before	7·38	35·5	—
		After	7·40	29·5	—
7	Siegle	Before	7·44	37·5	—
		After	7·24	47·5	—
8	Spargar	Before	7·39	31·0	52
		After	7·34	28·0	50
9	Armstrong	Before	7·38	41	—
		After	7·35	41	—
10	Fallon	Before	7·41	21	—
		After	7·35	21	—
11	Johnston	Before	7·35	39	—
		After	7·35	34	—
12	Robinson	Before	—	24	48
		After	—	17	49
13	Cumming	Before	7·50	22	52
		After	7·44	22	48
14	Brew 3 Stairs	Before	7·46	34	47
		After	7·46	40	48
15	Sherlock	Before	7·45	34	60
		After	7·42	43	52
16	Middleton	Before	7·46	21	51
		After	7·46	21	45
17	Williams	Before	7·54	30	57
		After	7·42	24	53
18	Altie	Before	7·47	—	51
		After	7·39	—	46

to these rules are extreme cases of heart failure such as Case 38, where the lactic acid content was so high that it was no longer compensated by the CO_2 loss. In such cases the lactic acid content of blood stands in inverse ratio to blood pH.

pH and lactic acid after standard exercise. In regard to the lactic acid, Table III, it can be stated that, broadly speaking, cases which show a low lactic acid content under resting conditions are cases which do not increase the lactic acid content after the standard exercise employed (see Cases 2,

10, 12, 13, 16).   As will have been seen from Table I, in normal cases the
variations of blood lactic acid at rest and after the standard exercise come
within the limit of margin of error of our method.   It may, therefore, be
assumed that this standard of exercise has not produced any appreciable
change in the blood lactic acid and pH.   These are cases which do not
exhibit any evidence of heart failure.   On the other hand, cases in which,
under resting conditions, the lactic acid is increased above normal fre-
quently react to the standard exercise by an increase of the lactic acid
level.   The pH is almost in every case lowered as the result of a standard
exercise.   Broadly, the more a case exhibits evidence of heart failure the
greater the difference of lactic acid between resting values, and after the
standard exercise.   A lowering of pH by 0·1 as a result of the standard
exercise is usually found in cases which exhibit pronounced evidence of
heart failure.

Discussion

Owles (13) suggested that lactic acid in the normal individual in the con-
dition of resting can be accounted for by the work the heart performs and
the respiratory mechanism.   A case of pronounced heart failure exhibits
abnormal features in many directions.   The percentage of oxygen saturation
in the venous blood is lower than normal.   This particularly is the case
after exertion.   This fact suggests a slowing of the blood-stream due to
cardiac inefficiency.   In addition, too, the time it takes for recovery after
exertion as expressed by increased oxygen consumption above normal values
is prolonged (Hill's Requirements).   This, too, is due to the accumulation of
lactic acid in the blood in abnormal quantities.   Owing to deficient oxygena-
tion during work the organism contracts a debt of oxygen which involves
accumulation of lactic acid in the blood.   Incidentally the slowing of the
blood-stream not only means that oxygenation of the tissue is taking place
under difficult conditions, but also that the removal of waste products such
as CO_2 from the tissues is hindered.   The accumulation of lactic acid in
heart disease is probably due to defective oxygenation.   But it may be
caused by another factor. CO_2 accumulation owing to heart failure in the
tissue of the respiratory centre may excite the mechanism which brings
about a low CO_2 blood-content and an alkalosis.   Anrep and Cannan (15)
have shown that in alkalosis the blood lactic acid level rises, the acid
forming a kind of buffer.   Eggelton and Evans (14) confirm this fact, and it
is possible the two factors combine to bring about a lacticaemia.   This may
be the reason why it is difficult to find, apart from extreme cases, a
relationship between lactic acid and pH.   However, whatever the factors
may be which are responsible for the accumulation of lactic acid in the
blood in cases of heart failure, the amount of lactic acid in the blood is
directly related to the severity of heart failure.

Conclusions

1. Under resting conditions lactic acid in the blood is increased in cases of heart failure.   The amount of lactic acid stands in a definite relation to the degree of heart failure.

2. Apart from extreme cases the pH of the blood is normal in different types of heart disease.

3. The amount of lactic acid formed after a standard exercise stands in a definite relation to the cardiac reserve power.   The greater the degree of heart failure the greater the amount of lactic acid formed by standard exercise.

We are grateful for the valuable help which Professor Roaf has given us in connexion with this paper.

REFERENCES

1. Shock, N. W., and Hastings, A. B., *Journ. Biol. Chem.*, Balt., 1934, civ. 565.
2. Earle, I. P., and Cullen, G. E., *ibid.*, 1929, lxxxiii. 539.
3. Barr, D. P., Himwich, H. E., and Green, R. P., *ibid.*, 1923, lv. 495.
4. Lewis, T., et al., *Heart*, Lond., 1913–14, v. 45.
5. Fraser, F. R., Ross, J. P., and Dreyer, G., *Quart. Journ. Med.*, Oxford, 1921–2, xv. 195.
6. Meakins, J., and Davies, H. W., *Respiratory Function in Disease*, Edinb., &c., 1925, 143.
7. Campbell, J. H. M., and Poulton, E. P., *Journ. Physiol.*, Lond., 1920–1, liv. 152.
8. Meakins, J., and Davies, H. W., *Respiratory Function in Disease*, Edinb. &c., 1925, 300.
9. Porges, O., *Wien. Med. Woch.*, 1911, xxiv. 1147.
10. Fraser, F. R., et al., *Quart. Journ. Med.*, Oxford, 1928–9, xxii. 1.
11. Hill, A. V., Long, C. N. H., and Lupton, H., *Proc. Roy. Soc.*, Lond., B. 1924, xcvi. 438.
12. Jervell, O., *Acta Med. Scand.*, Stockholm, 1929, lxxii. 262.
13. Owles, W. H., *Journ. Physiol.*, Lond., 1930, lxix. 214.
14. Eggelton, M. G., and Evans, C. L., *ibid.*, 1930, lxx. 273.
15. Anrep, G. V., and Cannan, R. K., *ibid.*, 1923–4, lviii. 244.

SKIN REACTIVITY TO GLYCERINATED VEAL BROTH AND ITS BEARING ON THE SPECIFICITY OF THE TUBERCULIN REACTION [1,2]

JULES FREUND AND P. D'ARCY HART

(From the Department of Pathology, Cornell University Medical College, New York City)

Introduction

THE use of glycerinated veal peptone broth (referred to here as G. V. B.), of the same composition as the culture medium commonly used in the preparation of old tuberculin (referred to as O. T.), and like the latter concentrated ten times by heat, has been advocated by some workers as a rational control for tuberculin skin tests. It has been assumed that if equal quantities of old tuberculin and of broth control are used, specific tuberculin reactions, that is, reactions caused by the specific products of the growth of the tubercle bacillus and presumably indicative of tuberculous infection, can be differentiated from any reactions caused merely by the broth medium contained in old tuberculin. If the reaction to the glycerinated veal broth is negative or is smaller than that to the old tuberculin, the tuberculin reaction is regarded as specific. The distinction is analogous to that between the true and pseudo-reactions of the Schick test.

Since, however, the majority of clinicians, in routine testing with old tuberculin, do not employ a broth control, it is important to know whether false positive reactions to ordinary doses of tuberculin, having the characteristic appearance and delayed onset, do in fact exist. If their incidence is significant the use of a control becomes imperative, and much of the epidemiological work that has been carried out on tuberculous infection is weakened in consequence. It should be possible to answer this question by testing a series of persons with old tuberculin and glycerinated veal broth, observing the frequency of reactions to broth, comparing the size and appearance of such reactions with those of the tuberculin reactions, and determining how far sensitivity to broth and to tuberculin are associated. Although there are several reports by workers in various countries on the occurrence of skin reactions to glycerinated veal broth, opinions have differed on the above points (see review by Hart (2)).

[1] Received July 12, 1935.

[2] The present communication makes it necessary to revise some of the statements made in a paper by one of the authors (Hart (2)) in this Journal.

Previous Investigations

Hart (2) himself elicited skin reactions similar in appearance to the characteristic delayed tuberculin reaction in a series of persons by the intra-cutaneous injection of G. V. B. Some of his observations are summarized as follows (see also Table):

Routine doses of O. T. were employed. In some cases the dose of G. V. B. was the same as that of O. T.; in others it was greater, in order to see whether the incidence of broth-reactions would be thereby increased. Tests were read on the second or third days. The subjects were clinically tuberculous and non-tuberculous patients.

The reactions to G. V. B. were found only in those positive to 0·1 mg. of O. T., out of 418 persons negative to this dose of tuberculin only one giving a reaction to the broth (dose 0·1 mg., 1·0 mg., or 10 mg.).[3] The single exception was positive to 1·0 mg. of O. T.

Of 166 persons positive to 0·1 mg. of O. T. a reaction to G. V. B. was obtained in as many as 156 (94 per cent.) when as much as 10 mg. of the broth were used: when 72 of these 166 persons were tested with 0·1 mg. of G. V. B. the percentage of broth-positives was reduced to 30. Of 150 different persons who were positive to 0·1 mg. of O. T. and had been tested with 0·1 mg. of G. V. B. a reaction to the broth was observed in 28 (19 per cent.).

Of 380 cases (including some already mentioned) in which equal doses of O. T. and G. V. B. were used 297 were positive to the tuberculin. In 295 of these 297 persons (98·3 per cent.) the corresponding reactions to the control broth were either negative or, if positive (38 cases), were of smaller size. The other two persons gave equal reactions to G. V. B. and to O. T., but were found to be positive when tested with a tuberculin prepared from a synthetic non-protein medium.

The intensity of the reactions in broth-sensitive persons was found in the main to run parallel with the intensity of the tuberculin reactions.

The property of eliciting the tuberculin-like skin reaction was found to be present in both the peptone fraction and the veal extract fraction of G. V. B. (see Appendix).

In other experiments (unpublished) no essential difference was found between reactions to equal quantities of unconcentrated broth and of broth concentrated to one-tenth of its original volume in the usual manner.

This work was based on six samples of G. V. B. made by the Wellcome Physiological Research Laboratories, Beckenham, England, according to method A (see Appendix), and one sample made by the Hoechst Laboratory, Germany. Six of the seven samples (including the German preparation) were active in varying degree, some being highly potent. From the results Hart concluded that sensitivity to G. V. B. was constantly associated with true tuberculin sensitivity, i.e. presumably with tuberculous infection, and suggested that nearly every tuberculin-sensitive individual would react to G. V. B. if a very active sample and an adequate dose were

---

[3] 0·01 mg., 0·1 mg., 1·0 mg., 10 mg., of O. T. or of G. V. B. correspond to 0·1 c.c. (the volume of fluid injected in the intracutaneous test) of 1 : 10,000, 1 : 1,000, 1 : 100, 1 : 10 dilutions, respectively.

used.   In seeking an explanation for this remarkable association he raised the question whether the tuberculin-like reactions of G.V.B. might have been caused by the introduction of adventitious tuberculous material either from the meat used, or during subsequent preparation.   Such an explanation, though not completely excluded, was deemed very unlikely in view of the number of samples used, and also because the findings supported those of other workers in France and Germany, one of whom (Doelter (1)) stated that he had satisfied himself that the skin activity of his broth was not due to tuberculous meat or to contamination during manufacture.   From the apparent constant association between sensitivity to G.V.B. and true tuberculin sensitivity Hart (3) drew the further conclusion that with the doses of O.T. used in routine testing the use of a broth control was unnecessary.

The high potency of G.V.B. noted in Hart's (2) paper received support from subsequent observations made both by himself and by an independent worker, using additional batches from the Wellcome Laboratories.   Nevertheless, it was considered advisable to test the possibility that the reactivity was due to tuberculous meat, and for this purpose muscle was obtained from a calf belonging to a herd of tuberculin non-reactors (1932).   Veal extract prepared from this source in the Bacteriological Department of University College Hospital Medical School, London, and sterilized either by autoclaving or by filtration, was tested on a series of tuberculin-sensitive persons, but was found to give entirely negative results.

At this point (1932) preliminary experiments in the Wellcome Laboratories showed that tuberculin adhered to filter candles and glassware with a degree of tenacity far greater than was generally recognized.   Long before this work Zieler (5) had, however, pointed out this property of tuberculin, and the consequent risk of contamination, in a paper that appeared to have been forgotten by the writers of textbooks.   It was found that saline or other bland diluting fluid that had been brought into contact with glassware or Berkefeld filters previously used for tuberculin, even if these utensils were subsequently thoroughly washed and autoclaved, gave clear-cut skin reactions in tuberculous guinea-pigs.   It was concluded that apparatus previously used for tuberculin should not be used for other immunological products : for example, the use of the same syringes for tuberculin tests and for Schick or Dick tests would be liable to give fallacious results.

These laboratory findings, which were published recently (Parish and O'Brien (4)), cast doubt on Hart's (2) earlier results, since, owing to the methods of preparation in use at that time, the possibility that the G.V.B. then employed had been contaminated with tuberculin could not now be excluded.   Accordingly a number of fresh batches of G.V.B. were put at his disposal by the Wellcome Laboratories.   In their preparation and use care was taken not to employ glassware that had previously been in contact with tuberculin, and new Berkefeld filter candles were used for filtration.

During 1933–4 Hart made experiments (unpublished) with these batches

of broth. The figures in three series of persons, each series tested with a different batch, may be given together (see also Table):

Fifty-two persons, a third of whom were clinically tuberculous, were injected intracutaneously with G. V. B. and with O. T. The broth was prepared according to method A (see Appendix), save that it was not concentrated ten times by heat, and doses corresponding to 10 mg. of the usual, concentrated, broth were used. The dose of tuberculin was 0·01 mg. The tests were read two days after the injection. Of the 52 persons tested, 39 were positive and 13 negative to the tuberculin. Four of the positives (10 per cent.) also gave reactions to the broth, the latter being smaller than the reactions to tuberculin.

While, therefore, a small number of broth-sensitive individuals was found in these series the incidence was much lower than that in the series previously published, though the dose of broth was as great. This finding suggested that contamination with tuberculin might have played a part in producing the high incidence of broth-positives found in the earlier experiments.

Meantime (1933) Freund, working independently, had also carried out experiments (unpublished) on cutaneous reactivity to glycerinated veal broth, obtaining results closer to those of Hart's more recent series than to those of his earlier series. The main points in Freund's work are summarized as follows:

A series of out-patients, medical students, nurses in training, and graduate nurses was tested simultaneously with O. T. and G. V. B., the latter being prepared by Gilliland Company, Marietta, Pennsylvania, according to method B (see Appendix), a method that avoids bacterial filtration. The tuberculin tests were made by injecting 0·01 mg. of O. T. intracutaneously, reading the test two days after the injection, and then injecting 1·0 mg. of O. T. if the first test was negative. The second test was also read two days after the injection. The out-patients received a single intracutaneous injection of 1·0 mg. of G. V. B. at the time of the first injection of tuberculin. The other persons were injected with equal amounts of tuberculin and broth, that is, they were given 0·01 mg. of G. V. B. with the first dose of O. T., and 1·0 mg. of G. V. B. if a second injection of O. T. was made; those finally classed as tuberculin-negative thus received 1·0 mg. of broth.

Of 41 out-patients tested, 38 were positive to O. T. and 9 of these (24 per cent.) were positive to G. V. B.; while of 368 medical students and nurses tested, 331 were positive to O. T. and 41 of these (12 per cent.) were positive to G. V. B. (see also Table). The reactions to the broth were found only in persons who reacted positively to the tuberculin. The area of inflammation was always less extensive at the site of injection of the broth than at the site of injection of the tuberculin, when equal amounts of these substances were injected. Even when, as in the group of out-patients, broth was given in larger amounts than tuberculin, its reaction was the smaller. Reactions to broth did not occur more frequently in persons strongly sensitive to tuberculin than in those who reacted weakly to the latter substance. The appearance of reactions to the broth was similar to that of the tuberculin reactions, save that the central papule seen in the stronger tuberculin reactions was absent.

These results are similar to those of Hart's (2) earlier, published, experi-

ments in the following respects : the reactions to broth were found only in tuberculin-positive persons ; they resembled the tuberculin reaction in appearance ; and their intensity was less than that of the accompanying tuberculin reactions.   On the other hand, the frequency of reactions to broth in this series was less than in Hart's series, and the intensity of the responses to broth and to tuberculin did not correspond.   The smaller incidence of broth reactions might have been partly due to smaller amounts of G. V. B. used, though it agrees with the similarly small incidence found in Hart's more recent, unpublished, experiments described above.

Present Investigation

The foregoing considerations showed the need for further clarification, and also made it desirable to check Freund's observations, using all possible precautions to avoid contamination.   It was considered advantageous that we should jointly carry out the investigation.

Two samples of G. V. B. were used, both prepared according to method B (see Appendix).   One (sample *G*) was obtained from Gilliland Company. The other (sample *GC*) was prepared in Cornell University Medical College, using glassware that had not been previously employed for work with tuberculin.   The syringes used for injection were new and were kept and sterilized separately.

Seventy-two patients (mainly adult) suffering from diseases other than tuberculosis were tested intracutaneously with 0·01 mg. of O. T. together with 1·0 mg. (14 patients) or 10 mg. (58 patients) of both *G* and *GC* batches of G. V. B.   The tests were read at one and two days after the injections. Of the 72 persons injected, 52 reacted positively to the tuberculin (0·01 mg.).   Of those tested with 1·0 mg. of the broth, one reacted to both batches *G* and *GC*, and one gave a scant reaction to batch *G* only.   Of those tested with 10 mg. of broth, one reacted to both *G* and *GC* : one gave a scant reaction to *G* only ; and two gave a definite, and one a scant, reaction to *GC* only.   The above seven reactions to G. V. B. consisted of redness and oedema over an area more than 5 mm. in diameter.   Some of them were visible at one day but faded before the second day ; others were greater at the second reading.   Some of them resembled tuberculin reactions in appearance ; others could be differentiated.   In addition to these reactions to G. V. B. there were three others consisting of definite erythema but with no oedema (dose 10 mg.).   Of the ten persons in all who reacted to broth (1·0 mg. or 10 mg.) nine were positive reactors to the single injection of 0·01 mg. of tuberculin.   The remaining patient, who gave a scant reaction to broth (10 mg.), was negative to tuberculin (0·01 mg.), but this is a small dose of tuberculin, and it is possible that the individual in question would have given a positive reaction to a larger dose.   (See Table).

A second group, composed of twenty-eight student nurses, was then tested. Since no significant difference in the incidence of reactions to the two

samples of G. V. B. had been observed in the first group, sample *G* was alone used in the present group. The nurses were tested with 10 mg. of the broth and with 0·01 mg. of O. T., and readings were made two days later. Those who were negative to 0·01 mg. of O. T. were then injected again with 1·0 mg. of this substance. Twenty-three of the group were found to be positive to the tuberculin test. Three of them showed reactions to the broth. In one case this reaction consisted of erythema and oedema ; in the other two there was a more extensive redness but no oedema. In the first case the tuberculin test was negative ; in the other two it was positive. The tuberculin test of the first nurse was extended by injecting 10 mg. of O. T. and at the same time a second dose of 10 mg. of the broth. The sites of injection were observed at one and two days. Definite erythema and oedema at the sites of both injections were seen at twenty-four hours : these were smaller, but still present on the second day. The grade of the reactions was approximately the same (tuberculin 28 × 25 × 1 mm., and broth 30 × 25 × 0·5 mm., on the second day. (See Table)).

In the 75 individuals of the two groups of the present series who reacted positively to routine doses of O. T. (0·01 mg. to 1·0 mg.) the reactions to G. V. B., where they occurred (11 cases, 15 per cent.), were smaller, even though the doses given were greater. The two individuals who reacted to the broth but were negative to the routine doses of tuberculin have already been mentioned. (Figures for the two groups together are given in the Table.)

Discussion

The results presented in this paper show that even when all precautions are taken to exclude the possibility of contamination with tuberculin, skin reactions are occasionally elicited by injection of glycerinated veal broth (1·0 mg. or 10 mg.). The appearance of these reactions sometimes resembles, at other times differs from, that of the tuberculin reaction. Furthermore, reactions to broth may have faded by the second day, when the tuberculin reaction usually reaches its height.

The comparative infrequency of reactions to glycerinated veal broth in the present series supports the view that the high incidence previously reported by Hart, using much the same dosage, was due to contamination of the broth with tuberculin. This possibility does not, however, invalidate his observation that reactions to broth (dose from 0·1 mg. to 10 mg.) did not occur in 417 of 418 persons who were negative to 0·1 mg. of old tuberculin. The additional figures given in the present paper (see Table), providing another 78 cases, negative to 0·01 mg. or 1·0 mg. of tuberculin and tested with equal or larger amounts of broth (up to 10 mg.), confirm this observation, with the two exceptions cited. The first exception, reacting to 10 mg. of broth but negative to 0·01 mg. of tuberculin, was unfortunately not tested with larger doses of tuberculin. The second exception, when injected

with equal amounts (10 mg.) of tuberculin and broth, gave equal reactions, suggesting that the reaction to this large dose of old tuberculin was non-specific.

It has been stated that when tested with the usual routine doses of old tuberculin (0·01 mg. to 1·0 mg.) the 75 persons in the present series who reacted positively showed either no response to the broth (1·0 mg. or 10 mg.) or a reaction smaller than that given to the tuberculin. Presumably, therefore, the positive tuberculin reactions in these persons were specific and due to something more than the broth ingredients of the material. In other words, they were true, not false, positives.

Since, with the two exceptions mentioned, reactions to glycerinated veal broth have not been seen in persons negative to routine doses of old tuber-culin but occur in a few persons positive to such doses, and since in these latter the positive tuberculin reactions are apparently specific, it seems that there is an association between skin sensitivity to the broth and true tuber-culin sensitivity, and presumably, therefore, between sensitivity to broth and infection by the tubercle bacillus. If this be the case, the use of equal amounts of glycerinated veal broth as a control for old tuberculin, when the latter is given in routine doses (0·01 mg. to 1·0 mg.), is unnecessary because it is redundant. These remarks do not, however, apply to doses of old tuberculin greater than 1·0 mg.

The practical absence of false positive reactions to the usual doses of old tuberculin, if generally applicable, strengthens the validity of the great mass of clinical and epidemiological work in which a positive tuberculin reaction, obtained with old tuberculin and without an accompanying control test, has been assumed to indicate tuberculous infection.

It is desirable to revise some of the points in Hart's (2, 3) earlier work on skin reactivity to glycerinated veal broth in the light of the observations recorded in the present paper. His statements that reactions to broth occur, that sensitivity to this substance is constantly associated with true tuberculin sensitivity, and that the use of broth control in routine tuber-culin testing is unnecessary, are substantiated. On the other hand, the high incidence of reactions to broth found by him, the constant resemblance of such reactions to the tuberculin reaction, and their parallelism of in-tensity with the latter, are not confirmed. By contrast, the incidence of reactions to broth in the present series is of the same order as that found in Hart's more recent, unpublished, series and also in Freund's earlier series. Under the circumstances it is proper to ascribe these differences, in part at least, to the use, in the earlier observations of Hart, of material con-taminated with tuberculin.

Throughout this paper the term tuberculin skin reaction has referred to the characteristic delayed persistent inflammatory skin reaction, reaching its height usually in two days, and it is in support of the specificity of this response to old tuberculin, when routine doses are given intracutaneously, that evidence has been presented. It is not disputed that various (erythe-

matous or urticarial) atypical non-specific reactions may also follow the injection of even small doses of old tuberculin, either immediately or in the course of a few hours, but such reactions have usually faded by the next day, so that confusion is avoided in practice by reading tuberculin tests two days after the injection. When referring to glycerinated veal broth in this paper the term reaction has been limited to delayed responses reaching their height one, two, or more days after the injection, but has not been limited to responses resembling the tuberculin reaction in appearance.

Reactions to Glycerinated Veal Peptone Broth (G. V. B.) in Relation to Tuberculin (O. T.) Reactions

In persons positive to tuberculin (dose 0·01–1·0 mg.)

	Number.		Result of broth test.		
		Dose of broth.	Positive.	Negative.	Per cent. positive.
Hart 1932	316 { 166 / 150	10 mg. / 0·1 mg.	156 / 28 } 184	132	58
Freund 1933	369 { 38 / 331	1·0 mg. / 0·01–1·0 mg.	9 / 41 } 50	319	14
Hart 1933–4	39	10 mg.	4	35	10
Freund and Hart 1935	75 { 52 / 23	1·0–10 mg. / 10 mg.	9 / 2 } 11	64	15

In persons negative to tuberculin (dose 0·01–1·0 mg.)

	Number.		Result of broth test.	
		Dose of broth.	Positive.	Negative·
Hart 1932	418	0·1–10 mg.	1*	417
Freund 1933	40	1·0 mg.	0	40
Hart 1933–4	13	10 mg.	0	13
Freund and Hart 1935	25 { 20 / 5	1·0–10 mg. / 10 mg.	1 / 1 } 2†	23

* This case, negative to 0·1 mg. of O. T., was tested further with 1·0 mg. and was found to be positive to this dose.

† One of these cases was tested with 10 mg. of G. V. B. but only with 0·01 mg. of O. T. The other case was negative to 1·0 mg. of O. T. but reacted equally to 10 mg. of O. T. and G. V. B., indicating non-specificity.

Summary

1. Experiments have been made on skin sensitivity to glycerinated veal peptone broth (G. V. B.), the usual control for old tuberculin, in relation to tuberculin sensitivity, in order to complement a series of similar experiments made by Hart (2). At that time the extreme tenacity of tuberculin, and the consequent risk of contaminating G. V. B. during the processes used in preparing the latter substance, were insufficiently recognized.

2. In the present series persons who have been tested intracutaneously with G. V. B., prepared with all possible avoidance of contamination with tuberculin, and used in doses of 1·0 mg. or 10 mg., have been found to give reactions in a small number of instances.

3. These reactions, when they have occurred in positive reactors to the usual routine doses of old tuberculin (0·01 mg. to 1·0 mg.), have been smaller than the corresponding tuberculin reactions, even though the doses of broth have been larger than those of tuberculin.   It is inferred that the positive tuberculin reactions in these cases were therefore specific, and not due merely to the broth content of old tuberculin.

4. Reactions to G. V. B. have only very rarely (twice in 496 cases, comprising the previous as well as the present series) been seen in individuals negative to routine doses of old tuberculin, even when the dose of broth (up to 10 mg.) has exceeded that of the tuberculin.

5. From this association of sensitivity to G. V. B. with true tuberculin sensitivity, and, therefore, presumably with tuberculous infection, it follows that the occurrence of reactions to G. V. B. does not affect the significance of positive reactions to routine doses (0·01 mg. to 1·0 mg.) of old tuberculin, and that consequently the use of broth controls in routine tuberculin testing is not necessary.

APPENDIX

Methods used in Preparation of Glycerinated Veal Peptone Broth (G. V. B.)

Method A.   Veal extract made by adding 1 lb. of veal, freed from fat and bone and minced, to 1 litre of cold tap-water containing 0·5 per cent. sodium chloride, boiling for one hour, filtering through wire and Dumas paper, and making up to original volume with tap-water.

Bacteriological peptone (Parke Davis) and glycerin dissolved in the veal extract to make 2 and 5 per cent. respectively.   Reaction adjusted to pH 7·7 by adding $10 \times N/1$ sodium hydroxide.   Mixture boiled for five minutes, filtered through paper, bottled, autoclaved for half an hour at 15 lb. pressure, and stored.

When required the broth is concentrated ten times over steam and filtered through Berkefeld candles.

Before use the broth is diluted to required strength with 0·5 per cent. phenol-saline; and 0·1 c.c. is injected intracutaneously.

Method B.   Veal; bactopeptone (Parke Davis) 1 per cent.; sodium chloride 0·5 per cent.; glycerin 5 per cent.; reaction adjusted to pH 7·8–8·0.

Sterilized in Arnold sterilizer at 100° C. on three days; evaporated to one-tenth original volume; filtered through Chardin paper; sterilized at 100° C. on three successive days.

Before use the broth is diluted to required strength with normal saline; and 0·1 c.c. is injected intracutaneously.

REFERENCES

1. Doelter, W., *Monatschr. f. Kinderh.*, Leipz., 1926, xxxiv. 198.
2. Hart, P. D'Arcy, *Quart. Journ. Med.*, Oxford, 1932, N.S., i. 49.
3. Hart, P. D'Arcy, *Med. Res. Coun. Spec. Rep. Ser.*, Lond., 1932, No. 164, p. 46.
4. Parish, H. J., and O'Brien, R. A., *Brit. Med. Journ.*, Lond., 1935, i. 1018.
5. Zieler, K., *Deutsche med. Wchnschr.*, Leipz., 1911, xxxvii. 2075.

p.
w
th
S
si
p
di
th
ar

ex
rh
ar
it
fu
ec
of
rh
a

n
st
to
gi
th
ca
ir
te

H

SOME TYPES OF RESPIRATION IN THE NEUROSES [1]

By RONALD V. CHRISTIE

(From the Department of Medicine, McGill University Clinic, Royal
Victoria Hospital, Montreal)

With Plates 28 and 29

In the minds of most of us the term respiratory neurosis conjures up a picture either of those rather rare cases of hysterical hyperventilation tetany which have been described in the literature, or of those cases which during the Great War, were labelled 'War Neurasthenia', 'D. A. H.', 'Effort Syndrome', or 'Irritable Heart'. Yet most clinicians will agree that occasionally cases crop up which do not fall into either of these two groups, but present such bizarre respiratory complaints that, often as an admission of diagnostic impotence, they are labelled as respiratory neuroses. We believe that the incidence of these cases is much greater than is generally supposed, and that some simple laboratory tests may be of diagnostic significance.

The respiratory system, if we confine this term to the process of gaseous exchange in the lungs, is unique in that although it is primarily one of the rhythmic involuntary processes, it is also very sensitive to voluntary control, and to the emotions. In fact, there is hardly an emotion which has not its obvious respiratory manifestation. It is also unique in that changes in function can be very easily and accurately recorded. Most hospitals are equipped with a recording spirometer as is used for the routine estimation of the basal metabolic rate. During this estimation the respiratory depth, rhythm, and level are recorded (Plate 28, Fig. 1), and we believe that such a tracing shows characteristic changes in the respiratory neuroses.

In all we have collected thirty-five patients in whom clinical diagnosis of neurosis was made, who had respiratory symptoms referable to no demonstrable organic lesion, and who showed the respiratory irregularities about to be described. As case protocols to be of any value would have to be given in considerable detail, they have been omitted. We have divided these cases into the anxiety neuroses and the conversion hysterias. Our cases have naturally fallen into two groups—the anxiety neurosis with an irregular shallow type of respiration, and the conversion hysterias where the tendency is to hyperventilate.

(a) *The anxiety neuroses.* To this group belong the cases of 'Irritable Heart' or 'Effort Syndrome', which, although usually classified as cardiac

---

[1] Received September 3, 1935.

neurosis, are as essentially respiratory. The syndrome has been frequently described as a well-defined clinical entity. The invariable symptom is breathlessness, but most cases also complain of palpitation, giddiness, sweating, and precordial pain, all exaggerated by exercise. The breathlessness is reflected by a tendency to rapid and shallow breathing rather than a true hyperpnoea. In fact, the shallowness of the respirations may in severe cases lead to anoxaemia and cyanosis, naturally relieved by oxygen. During the War, when these cases were so plentiful, the recording spirometer had not yet reached its present popularity, and it is probably for this reason that the characteristic changes which occur in the respiratory level and rhythm have not been appreciated.

In Plate 28, Fig. 2, is shown a respiratory tracing from a typical case of ' Effort Syndrome ' whose symptoms had persisted since the Great War. By inspection of his thorax it was only possible to say that his breathing was rapid and shallow, but the tracing brings out several points which we believe to be even more characteristic of this condition : (a) an irregularity of the respiratory level ; (b) an irregularity of respiratory depth ; (c) a less marked irregularity of respiratory rate.

In Plate 28, Fig. 3, are tracings from four similar cases, the onset also dating from the Great War, but of somewhat less severity. Case R. G. (upper right) had symptoms when subjected to the mildest emotional stimuli, even when at rest, while the other three only complained of nervousness, dyspnoea, and palpitation on the mildest exertion. Fig. 4 is from a case occurring in civil life. As his history is of special interest we will describe it in some detail.

Case E. G. Male. Aged 46. He was working in a quarry when a 2,000 lb. chain fell on the back of his neck, and had he not clutched the automatic carrier he would have been thrown some 40 ft. to the ground below. The symptoms which persisted after this accident were vague pains throughout his chest, breathlessness on the slightest exertion, sweating, and a feeling of weakness in his right leg. His pulse-rate at rest was between 84 and 95 per minute. On examination the only significant finding was a complete absence of costal movement, his breathing being wholly through the diaphragm. Although radiograms of the cervical vertebrae were negative, a tentative diagnosis of a lesion in the cord at the level of the fifth cervical vertebra was made, as such a lesion might lead to paralysis of the intercostals with the phrenics left intact, and thus account for his diaphragmatic breathing. He obtained a pension, and we saw him for the first time two years later, his condition having remained unchanged. His breathing was still purely diaphragmatic in type, but he gave the peculiar respiratory tracing shown in Fig 4, which we had previously found to be typical of the anxiety neuroses—an extreme irregularity in respiratory depth, rhythm, and level with an inability to co-operate in any form of respiratory gymnastics. At B he inspires when told to expire ; at C there is also no co-operation, and he could only hold his breath for ten seconds at D and E. At F, when told to breathe rapidly and deeply he breathed slowly and shallowly. At first sight

a diagnosis of neurosis in this case seemed somewhat far fetched, considering that it is impossible for a normal individual consciously to inhibit thoracic respiration, but we were able to prove this point by giving him an oxygen-carbon-dioxide mixture to rebreathe.   His diaphragmatic excursion steadily increased under this stimulus.   Respirations became more and more strained and irregular until ultimately a period of complete apnoea appeared, lasting about five seconds.   He developed a coarse tremor of the hands and face, and the inhibitory mechanism then suddenly broke down. He burst into floods of tears, and breathed freely with all his thoracic musculature.   Two hours later he was back to his diaphragmatic breathing.   It is of interest that an analysis of the arterial blood in this case showed a slight but real impairment of haemo-respiratory exchange, the oxygen saturation being only 89·5 per cent.   There was no significant impairment of CO_2 excretion.   Presumably this impairment of oxygenation is due to the inefficiency of rapid and shallow breathing.

The tracing in the top left-hand corner of Plate 28, Fig. 4, is of a case who actually had a fracture dislocation at the level of the fifth cervical vertebra. His respiratory tracing is perfectly regular and normal, but with paralysis of all his muscles of expiration he is unable to expel any reserve air, his vital capacity consisting solely of complemental air.

In Plate 28, Fig. 5, are shown tracings from three other cases of anxiety neurosis, in decreasing severity from right to left, which originated in civil life.   Case A. A. was a pharmacist who was aware of the fact that he had extensive coronary disease and was in constant fear of a sudden exitus, while with the other two the problem was more social than physical.

Altogether we have had thirteen such cases during the past two and a half years, all of them showing the same symptoms of dyspnoea, nervousness, sweating, and tachycardia in varying degrees, and all showing this irregular type of respiratory tracing.   Five of them were old cases of 'War Neurasthenia' or 'Effort Syndrome', and most of the thirteen had provisional diagnosis of either thyroid disease or dyspnoea and tachycardia of unknown origin.

(b) *The conversion hysterias.*   The other group of the respiratory neuroses which can be differentiated consists of the hysterias.   The signs and symptoms are very characteristic.   Almost invariably the subject complains of an inability 'to get enough air into the lungs'.   There is a sense of oppression which borders on a feeling of suffocation.   In the milder cases the response to this sensation is a series of deep sighing respirations, or in severe cases a paroxysm of hyperventilation leading to 'Hyperventilation Tetany'. The psychogenic factor underlying the neurosis in these cases is as complicated and varied as in any group of conversion hysterias, and we will not attempt to describe them.   Suffice it to say, that in all our cases there was ample evidence of a psychogenic background.

In Plate 29, Fig. 6, is shown an extreme case, who on the slightest provocation would have a paroxysm of deep and rapid breathing of such severity

that within a few minutes she would exhibit all the signs and symptoms of an acute gaseous alkalosis. The left-hand tracing in Fig. 6 shows such an attack precipitated by making her breathe into the spirometer. The minute volume respired increased about eight-fold to between 45 and 50 litres per minute with an increased excretion of carbon dioxide sufficient to produce all the signs and symptoms of acute tetany. At this stage the patient could not be roused and showed positive Trousseau and Chvostek signs, with a pulse-rate of 140 per minute. Her alveolar CO_2, taken by means of an automatic sampler (2), had fallen from 40 to 23 mm. of Hg, which, if we allow a fall of 5 vols. per cent. in the CO_2 content of the plasma, corresponds in her case to a change in pH from 7·38 to 7·62, which would be ample to account for her symptoms of alkalosis. The CO_2 content of her venous plasma fell from 60·7 to 54·6 vols. per cent. during the attack, but of course these figures can only be taken as a vague index of what was happening in the arterial blood. After the attack she would obviously hypoventilate for a while and then regain consciousness. The right-hand tracing in Fig. 6 is of a similar attaek, but in this case the soda-lime scrubber was removed from the spirometer, so that carbon dioxide was allowed to accumulate. Under these conditions she obviously could not develop her gaseous alkalosis by any amount of hyperventilation. She evidently realized it was a hoax and got so annoyed that she almost wrecked the spirometer.

In Plate 29, Fig. 7, are shown tracings from three examples of a more common type where the increase is in respiratory depth rather than rate. Between the deep sighing respirations are interposed breaths of normal depth. In the left-hand tracing the rate is decreased, although this is not common. The deep breaths are actually maximal inspiratory efforts and correspond closely with the vital capacity, but the resultant hyperventilation is insufficient to yield any symptoms of tetany. The air hunger of these cases is also reflected by their inability to hold their breath.

In Plate 29, Fig. 8, are shown four more cases, in diminishing severity, the lower right tracing being of the type one might expect from a normal though nervous individual.

It should be emphasized that the tracings shown in these figures have been chosen to demonstrate the various stages of the respiratory neuroses, from the obviously pathological to the border-line case, and do not represent the most spectacular of our series.

The Incidence of the Respiratory Neuroses

Thirty of the thirty-five cases in our series were diagnosed as respiratory neuroses during the years 1933 and 1934, but it is impossible to draw any significant conclusions as to the incidence from these figures. More significant, perhaps, is an analysis we have made of 1,500 consecutive tracings which were made for the routine estimation of the basal metabolic rate. Of these 104, or 6·9 per cent., were suggestive of a respiratory neurosis from the

respiratory criteria we have described, 79 falling into the 'anxiety' group and 25 into the hysterical or hyperventilating group.   An examination of the case records of these cases showed that in 55 a neurosis was diagnosed or indicated as probable.   In 35 there was no mention of neurosis, but the cases were discharged undiagnosed, and in only 14 was a definite diagnosis made with no mention of neurosis.   These figures are certainly suggestive of a higher incidence of the respiratory neuroses than is generally supposed.

Discussion

It must be emphasized that we in no way claim that all cases who have a respiratory neurosis will give a typical respiratory tracing.   We do claim that these respiratory irregularities, if sufficiently pronounced, are diagnostic of a respiratory neurosis, and that the incidence of these cases is much greater than is generally supposed.   If the irregularities are less pronounced, as in Figs. 3 and 8, the tracings can only be used as suggestive evidence.   A nervous individual with no actual neurosis will sometimes give a tracing of this type, but the irregularities usually disappear when the test is repeated.   In emphysema, also, the respiratory level is usually somewhat irregular (2), but it does not need a respiratory tracing to differentiate emphysema from a neurosis.   It is of interest in this respect that of the fourteen cases described above, who had respiratory tracings suggestive of a neurosis and yet nothing in their case histories to support such a diagnosis, four were diagnosed as advanced emphysema.

It is surprising that the use of the spirometer, in establishing these irregularities has not been appreciated.   The rapid and shallow breathing which occurs in 'Effort Syndrome' is quoted in most of the text-books, but no mention is made of the even more typical irregularities of level and depth. These cases are usually suspected of thyroid disease on account of the nervousness, tachycardia, and sweating, and in our experience their basal metabolic rate (by the Douglas bag technique) is usually raised by about 20 per cent.   But in hyperthyroidism it is rare to see a respiratory tracing which remains so irregular that it could be confused with an anxiety neurosis.

In the other group of cases—the hyperventilating or hysterical group— these tracings may also be of value, although in the extreme cases of hyperventilation tetany the diagnosis should be obvious from the first.   The less severe cases who merely complain of air hunger, which is not exaggerated by exercise, and an 'inability to get enough air into the lungs' are much more common, although one can find practically no mention of them in the literature.   Trumpr (4) has analysed the type of respiration in 101 cases of stammering, and in this group there are eleven with just this irregular type of deep breathing.   More recently Baker (1) has drawn attention to the frequency of 'sighing respiration as a symptom'.   She emphasizes the

nervous origin of this symptom complex, and we have no doubt that the cases she was dealing with are the same as our own.

Summary and Conclusions

1. Respiratory tracings taken by means of an ordinary recording spirometer are of value in the diagnosis and differentiation of certain types of respiratory neurosis.

2. The incidence of these types of respiratory neurosis is much higher than is generally supposed.

REFERENCES

1. Baker, D. M., *Lancet*, Lond., 1934, i. 174.
2. Christie, R. V., *Journ. Clin. Invest.*, 1934, xiii. 295.
3. Haldane, J. S., and Priestley, J. G., *Respiration*, Oxford University Press, 1935.
4. Trumpr, M., University of Pennsylvania, Philadelphia, 1928.

DESCRIPTION OF PLATES 28–29

PLATE 28, FIG. 1. Respiratory tracing from a normal individual. Tracing reads from right to left and is obtained by means of an ordinary recording spirometer into which the subject breathes. The carbon dioxide exhaled is absorbed so that the slope of the broken line (the 'respiratory level') represents the rate of oxygen consumption.

FIG. 2. Respiratory tracing from a case of 'Effort Syndrome'. Note irregularity in rate, depth, and level of respiration. (Tracing reads from left to right.)

FIG. 3. Respiratory tracings from 4 cases of 'Effort Syndrome'. (Tracings read from right to left.)

FIG. 4. Respiratory tracing from a case of 'Effort Syndrome' with pure diaphragmatic breathing which had been ascribed to a cord lesion at the level of the 5th cervical vertebra. The tracing in the upper left corner is from a case who had such a lesion and in consequence was incapable of any active expiratory effort. Note the absence of any reserve air when the vital capacity is recorded.

PLATE 29, FIG. 5. Respiratory tracings from 3 cases of 'Effort Syndrome' originating in civil life. (Tracings read from right to left.)

FIG. 6. Respiratory tracings from a case of 'Hyperventilation Tetany'. The left-hand tracing (which reads from right to left) is of a typical attack where the respiratory minute volume increased to 50 litres a minute and the patient presented all the classical signs of acute tetany. The right-hand tracing (which reads from left to right) is of a similar attack of hyperventilation in which the increased elimination of carbon dioxide was prevented by removing the soda-lime absorbent from the spirometer. No symptoms of tetany ensued, although the patient feigned unconsciousness.

FIG. 7. Respiratory tracings from 3 cases of the hyperventilating or hysterical type of respiratory neurosis. Note the periodic deep inspirations equivalent in depth to the vital capacity and inability to hold the breath.

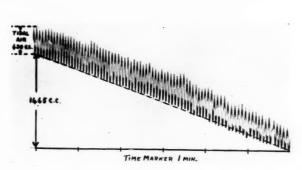FIG. 8. Respiratory tracings from 4 mild cases of the hyperventilating or hysterical type of respiratory neurosis.
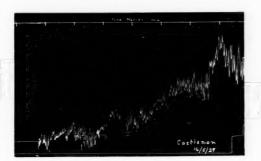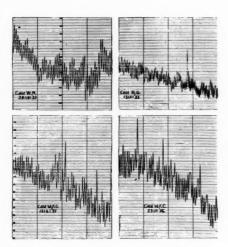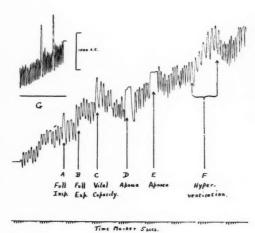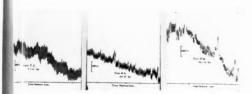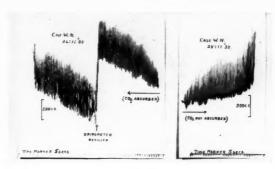
FIG. 1

FIG. 2

FIG. 3

FIG. 4
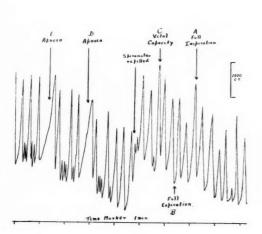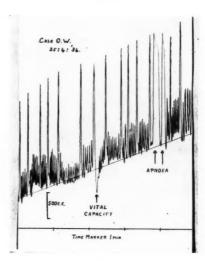
Fig. 5

Fig. 6

Fig 7 a
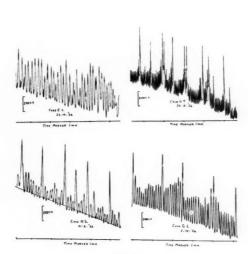

Fig. 7 b

Fig. 7 c

Fig. 8

ar
be

Qu

A

M
T

th

M

PROCEEDINGS OF THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

1935

TWENTY-NINTH ANNUAL GENERAL MEETING

THE TWENTY-NINTH ANNUAL GENERAL MEETING was held in London on Friday and Saturday, June 7 and 8, 1935, at the Royal Society of Medicine. The attendance book for the meeting was signed by 216 members. The proceedings began at 10 a.m.

The President, Professor T. Wardrop Griffith, was in the Chair.

The Minutes of the last Annual General Meeting, having been published in the *Quarterly Journal of Medicine*, were taken as read and confirmed.

Treasurer's Account. Dr. Letheby Tidy, Hon. Treasurer, presented the Annual Accounts which were adopted. They showed a balance of £238 5s. 4d.

Selection of Place of Meeting for 1936. A letter was read from Professor G. R. Murray, on behalf of the local Members, inviting the Association to meet in Manchester. The invitation was cordially accepted.

Election of Officers

President. Dr. H. Morley Fletcher was elected President. On his election he took the Chair, and expressed the thanks of the Association to the retiring President.

Election of Honorary Members, Officers, Executive Committee, Extra-Ordinary Members, and Ordinary Members followed.

Executive Committee

President. Dr. H. Morley Fletcher.

Treasurer. Dr. H. Letheby Tidy.

Secretary. Professor L. J. Witts.

Members for England:
Sir J. Charlton Briscoe.
Dr. J. le F. C. Burrow.
Professor A. W. M. Ellis.
Dr. A. G. Gibson.
Dr. A. W. Stott.
Dr. K. D. Wilkinson.

Members for Scotland:
Dr. J. Carslaw.
Dr. J. D. Comrie.
Dr. W. E. Foggie.

Members for Ireland:
Dr. L. Abrahamson.
Dr. E. T. Freeman.
Dr. Rowland Hill.

Honorary Members:

Professor T. Wardrop Griffith (President 1934–5).
Lord Dawson of Penn (President of the Royal College of Physicians).
Professor Sir F. Gowland Hopkins (President of the Royal Society).
Dr. Robert Hutchison (President of the Royal Society of Medicine).

Extra-Ordinary Members:

Professor E. Bramwell.
Professor J. G. Emanuel.
Dr. A. Dingwall Fordyce.
Dr. C. H. Melland.
Professor J. A. Nixon.
Dr. E. A. Saunders.
Dr. R. Travers Smith.
Dr. H. Thursfield.

Ordinary Members:

Ronald Winston Brookfield, M.D., Assistant Physician, Royal Southern Hospital, Liverpool.

James William Brown, M.D., Physician, Grimsby and District Hospital, Cleethorpes.

Thomas Howard Crozier, M.D., Physician, Belfast Infirmary, Belfast.

John St. Clair Elkington, M.D., Physician, St. Thomas's Hospital, London.

Neil Hamilton Fairley, M.D., Assistant Physician, Hospital for Tropical Diseases, London.

Ronald Thomson Grant, M.D., Director, Clinical Research Unit, Guy's Hospital, London.

Norman Kletz, M.R.C.P., Assistant Physician, Royal Infirmary, Manchester.

James Livingstone Livingstone, M.D., Physician, King's College Hospital, London.

Thomas Kay Maclachlan, F.R.F.P.S., Assistant Physician, Royal Infirmary, Glasgow.

Alan Aird Moncrieff, M.D., Physician, Middlesex Hospital, London.

William Ritchie Russell, M.D., Assistant Physician, Royal Infirmary, Edinburgh.

Kenneth Shirley Smith, M.D., Assistant Physician, Charing Cross Hospital, London.

Geoffrey Thompson, M.D., Assistant Physician, Royal City of Dublin Hospital, Dublin.

John Richard Hugh Towers, M.D., Assistant Physician, General Infirmary, Leeds.

Death of Honorary Member. Before passing to the scientific business the President referred to the loss the Association had sustained by the death of Sir John Rose Bradford, an Honorary Member.

SCIENTIFIC BUSINESS

Friday Morning

1. Dr. L. S. T. Burrell described *The Healing of Tuberculous Cavities of the Lung without Surgical Intervention*. Modern radiography often reveals cavities which would not otherwise be detected in a tuberculous lung, and it is now possible to close some of these by surgical means even if pneumothorax fails. A cavity is definitely a source of danger, but one should resist the modern tendency to try to close it at all costs, because the treatment is often more dangerous than the cavity. Skiagrams were shown to illustrate how cases, even with extensive cavitation, might heal by simple medical means. If, therefore, the disease does not appear to be spreading it is usually wise to hesitate before advising some thoracoplastic operation.

2. Dr. F. G. Chandler discussed *The Pleura and the Behaviour and Ultimate Fate of Chronic Pleural Effusion*. He first made certain observations clinical, radioscopic, and thoracoscopic on the behaviour and reaction of the pleura, with its content of air, fluid, sterile, and tuberculous pus and fibrin. These were illustrated by paintings made of the thoracoscopic appearances. The normal appearance was shown, the inflamed appearance described, deposition of fibrin, the formation of craters, the thick deposit of white fibrin, the fibrin body or pleural mouse, and obliterative pleurisy. Secondly, he submitted reasons for the conservative handling of chronic pleural effusions. Several examples were shown of effusions which persisted from five to as much as sixteen years, with the patient in perfect health. These effusions could be thick pus, and even

contain tubercle bacilli, with no detriment to the health of the patient; in fact, they might serve as an excellent collapsing medium for the lung. One trouble about these effusions was that it was impossible to know how long they would persist, even if the pleura was thick and the fluid purulent. Therefore, if there was a possibility of the fluid absorbing and the lung re-expanding before complete healing had probably taken place, it was better to replace the fluid by oil. Otherwise, the less interference with the fluid the better.

DR. E. T. FREEMAN thought that the determining factor in the treatment of chronic pleural effusions was the rigidity of the mediastinum. DR. BURRELL agreed with DR. CHANDLER that amyloid disease rarely, if ever, developed in cases of chronic pleural effusion, but was the result of disease of the lungs themselves.

3. PROFESSOR L. ABRAHAMSON read a paper on a *Case of 'Honeycombed' Lungs with Scleroderma*. The patient, a female, aged 37, was admitted to hospital on 27.3.34 for weakness and swelling of the ankles. She had complained all her life of dyspnoea, with cough and sputum for some years. Examination showed subcrepitant râles over the bases of both lungs and X-ray examination yielded a peculiar appearance of honeycombing of both lungs. Two months after admission scleroderma set in; first it involved the face, then the neck, hands, and feet; fingers and toes became gangrenous. Remittent pyrexia was present until 10.12.34, when the temperature became normal, remaining so until death supervened on 12.2.34. Autopsy showed a peculiar honeycombing of both lungs with air spaces averaging half a centimetre in diameter. Spaces beneath the pleura had raised this membrane into bullae, of which the largest measured 2 cm. in diameter. The walls of the spaces consisted of dense fibrous tissue. The condition suggested a congenital origin.

DR. PARKES WEBER regarded the case as one of congenital honeycombing of the lung with acquired streptococcal infection; the scleroderma and the gangrene were the result of the toxaemia. DR. H. BARBER referred to another case in which scleroderma had followed streptococcal infection.

4. DR. MANSON-BAHR exhibited a series of lantern slides and drawings illustrating *The Diagnosis of Hepatic Amoebiasis and its Pulmonary Complications*. In sections made through the base of an amoebic ulcer in the large intestine, individual *E. histolytica* may be demonstrated within the lumen of the capillary vessels in the submucosa; thence they are swept by the portal blood-stream into the liver where they can be demonstrated in microscopic sections. The various stages in liver abscess formation next ensue and finally, after rupture through the diaphragm, the secondary amoebic abscesses of the lung may be mistaken for all manner of pulmonary diseases.

A lively discussion followed in which DR. A. F. HURST and PROF. G. R. MURRAY referred especially to the frequent confusion of amoebic colitis and malignant disease. PROF. A. W. M. ELLIS commented on the occurrence of cases of amoebic hepatitis in this country and DR. J. W. MCNEE on the importance of repeated search for amoebae in ulcerative colitis. DRS. PATRICK, TIDY, FREEMAN, and the President also spoke. DR. MANSON-BAHR in reply protested against implications that he was too tropically minded, a view which no one had seriously maintained.

5. DR. CLIFFORD HOYLE described *The Heart in Chronic Lung Disease*. If the heart is involved at all in chronic lung disease it is not easy to decide by clinical methods the degree of involvement. The crux of the problem is really the presence or absence of enlargement, and this is best determined by radiology. An analysis was given of the cardiovascular features in a series of seventy cases of chronic bronchitis and emphysema. Symptoms were equivocal, and physical signs rarely pointed to involvement of the heart. Hypertension was a common association. Normal rhythm was the rule throughout its course and the pulse-rate was rarely excessive. Radiological evidence of enlargement of the right heart, chiefly of the right ventricle and conus pulmonalis, and of engorgement of the large pulmonary vessels was obtained in about half the cases. Congestive heart failure was seldom seen, though it was sought for. When present it was often accentuated by coincident hypertension. The prognosis seemed to be worse than in congestive failure from other causes, and digitalis proved of doubtful value.

DR. POULTON was surprised at the high percentage of patients with harsh expiration, as in his opinion the cardinal sign of emphysema was weakness of the breath sounds.

PROF. WARDROP GRIFFITH said that enlargement of the conus arteriosus was the commonest cause of upward extension of the cardiac dullness, as had now been proved by the use of X-rays. DR. T. JENNER HOSKIN also commented on this point.

DR. IVOR DAVIES and PROFESSOR G. R. MURRAY remarked on the frequency of bronchitis and emphysema in colliers and cotton workers, and the need for more data on the occupational incidence of this malady. SIR MAURICE CASSIDY thought that emphysema was the commonest cause of dyspnoea in later life, but DR. A. W. STOTT thought that it was nevertheless an uncommon cause of congestive heart failure.

DR. BURROW and SIR CHARLTON BRISCOE emphasized the importance of chest deformity in the production of cardiac symptoms and the value of respiratory exercises in treatment. DRS. EVAN BEDFORD, C. BRAMWELL, and CLAUDE WILSON also spoke.

2 p.m. to 4.30 p.m.

Demonstration of Cases in the Special Departments and New Wards of the Middlesex Hospital.

4.30 p.m. *Afternoon Session at the Middlesex Hospital*

1. DR. T. IZOD BENNETT reported *A Case of Bilateral Breast Tumours Associated with Cranial and other Nerve Palsies.* The first symptoms were tumour-like invasion of both breasts, with paralysis of the left side of the palate, the left sterno-mastoid, the left trapezius and deltoid, and general loss of tendon reflexes. The blood picture was normal, but during the course of three weeks further paralysis developed, affecting the right phrenic nerve and various muscles of the limbs. Very shortly before death the blood picture changed to that of acute myeloid leukaemia. Leukaemic invasion of the breasts and leukaemic nerve palsies were discussed.

DR. MCALPINE thought that the neurological symptoms were the result of a toxic polyneuritis. DR. GORDON HOLMES felt that the symptoms were too variable to be due to a general toxaemia and were better explained by microscopical infiltrations of the pia-arachnoid.

2. PROFESSOR E. C. DODDS and DR. R. L. NOBLE (introduced by DR. H. E. A. BOLDERO) demonstrated *The Relationship between the Pituitary Gland, the Stomach, and the Blood Picture.* An extract of the posterior lobe of the pituitary gland was shown to produce on injection an extensive haemorrhagic lesion of the oxyntic cell area of the stomach, and also severe macrocytic anaemia associated with reticulocytosis and changes in the bone marrow. There was also evidence of an increased activity of the reticulo-endothelial system. From these and unpublished experiments it was concluded that the posterior lobe of the pituitary gland has a controlling influence over the stomach and blood picture.

DR. GORDON HOLMES compared PROFESSOR DODDS's findings with the ulceration of the alimentary tract which sometimes occurred with tumours of the midbrain, but PROFESSOR DODDS did not think the two conditions were identical. DRS. NAISH, LEYTON, and D. CAMPBELL also spoke.

3. DR. P. HAMILL showed cinema films illustrating the value of *Physostigmine and its Allies in Neuromuscular Disorders.* DR. LEYTON said that the effect of physostigmine could be prolonged by injection of solutions in oil. SIR W. LANGDON BROWN reminded the meeting that Gee and Gowers had used physostigmine in the treatment of spastic paraplegia. DRS. MCALPINE and YATES also spoke.

Annual Dinner. The annual dinner was held at the Mayfair Hotel. The President, Dr. H. Morley Fletcher, was in the Chair. The official guests included H.R.H. Prince Arthur of Connaught, and the Presidents of the Royal College of Physicians, the Royal College of Surgeons, and the College of Obstetricians and Gynaecologists. There were present 130 members and guests.

Saturday, 10 a.m., Morning Session

1. DR. J. EASON reported on *The Treatment of Acute Rheumatic Disorders by Streptococcus Antitoxin (Scarlatina).* The average age of his 37 patients was 24 years. In 27 cases recovery followed upon the administration of one dose, viz. 60 c.c. given in two equal amounts at an interval of 36 hours. In ten cases one such dose failed to effect stable recovery. The first six of these ten were subsequently treated by salicylate

of soda. The last four were given supplementary injections of the serum. The average duration of fever, following the initial injection of serum and including fever due to serum disease, was a fraction over twelve days.

This communication met with some criticism; Dr. K. D. Wilkinson never having seen a case of acute rheumatism which failed to respond to adequate doses of salicylate, and Dr. L. Findlay suggesting that the effects of the serum should have been more precisely indicated. Dr. Buckley suggested that those cases of acute rheumatism which did not respond to salicylates might be due to infection by attenuated tubercle bacilli. Dr. Parkes Weber advised trying treatment with serum in the subacute rheumatism of adults.

Dr. Eason, on replying, reiterated his opinion that sodium salicylate was often a tragic failure.

2. Dr. Bernard Schlesinger brought forward *Evidence of a Virus Aetiology in Acute Rheumatism.* This included the isolation by rapid centrifugalization of an elementary body from the inflammatory pericardial fluid obtained from cases of the most acute pericarditis a few hours after death. Suspensions of these elementary bodies were agglutinated by the serum of a number of cases of pronounced active rheumatism with nodules. Controls proved negative. The probable association of streptococci and a virus in the causation of acute rheumatism was discussed. Dr. Amies gave microscopic demonstrations of the virus and its agglutination, and Dr. Signy an histological section of an Aschoff node showing inclusion bodies in one of the cells.

Sir Thomas Houston, while impressed by Dr. Schlesinger's communication, reaffirmed his opinion of the importance of streptococcal infection in rheumatism.

3. Dr. K. Harris discussed the results of a follow-up for two to four years of *100 Cases of Heart Disease with Normal Rhythm Complicating Pregnancy.* Great importance should be attached to the exercise tolerance and a careful history should be taken regarding any break-down of exercise tolerance during previous pregnancies. Earlier and earlier break-down of exercise tolerance in successive pregnancies is serious ; early break-down in a primigravida is of grave import. In eighteen patients with congestive failure the subsequent mortality was greater than in those without congestion ; primigravida with congestive failure did worse than multiparae with congestion. Induction of premature labour was successfully carried out in two cases of congestive failure, which were progressive in spite of medical treatment ; in one the congestion rapidly cleared up after emptying the uterus. Short intervals between pregnancies seem to increase the risk of congestive failure during pregnancy. All, except 3, were followed up for two years, and 3 for four years ; 10 were free of symptoms, 34 unchanged, 38 were worse, and 15 dead.

Dr. C. Bramwell emphasized the value of antenatal supervision. Dr. J. M. H. Campbell said that the great advantage of Caesarean section at term was that it enabled sterilization to be performed. Dr. Starling remarked on the frequency with which cardiac mischief was first detected in pregnancy.

4. Professor L. S. P. Davidson with Drs. H. W. Fullerton, and R. M. Campbell (introduced), discussed *The Incidence of Anaemia among the Poor in the North-East of Scotland.* Haemoglobin estimations of approximately 4,000 individuals of the poorest classes in Aberdeen and the North-East of Scotland showed that, despite the low iron content of the diet, anaemia was frequent in only two groups : (1) infants between the ages of 11 and 24 months : 29 per cent. were moderately anaemic (Hb 60–74 per cent.), and 7 per cent. severely anaemic (Hb less than 60 per cent.; (2) women of the reproductive age : 17 per cent. were moderately anaemic (Hb 70–80 per cent.) and 16 per cent. severely anaemic (Hb less than 70 per cent.). Professor Davidson thought that the diets of the very poor could cheaply be made more adequate by the prescription of a glass of milk a day and medicinal doses of iron.

Drs. Naish and Spence remarked on the importance of infections in childhood in aggravating the anaemia—a vicious circle, inasmuch as anaemia predisposed to infection. It was therefore important to begin treatment early. Dr. Tidy wondered whether there was a sexual factor other than pregnancy and menstruation, and did not believe that the disappearance of chlorosis was satisfactorily explained by changes in diet.

5. Dr. Donald Hunter and Dr. J. F. Brock (introduced) reported *Quantitative*

Studies of the Fate of Iron Administered by Mouth. A method was described for studying directly the amount of iron retained by the human body when iron is administered by mouth. The amounts of iron retained by anaemic and non-anaemic patients receiving 60 to 90 grains a day of iron and ammonium citrate or of Pil. Ferri Carb. were considerably greater than has been inferred from the indirect method of calculating the haemoglobin increase in patients similarly treated for so-called iron-deficiency anaemia. DR. HUNTER commented on the value of ferrous salts in treatment, but DR. TIDY had found that they often led to gastric disturbance. PROFESSOR DAVIDSON found difficulty in believing that so much iron was retained, and wondered why the patients were not converted into pillars of iron. DR. N. MORRIS confirmed DR. BROCK's results. DR. PARKES WEBER also spoke.

6. PROFESSOR L. J. WITTS reported *Two Cases of Agranulocytosis after taking Yeast Vite,* and another after taking Cachet Faivre; both of these preparations contained pyramidon. Of five cases of agranulocytosis in which he had obtained a careful history, four had taken pyramidon and one had taken salol. Both pentnucleotide and liver extract had proved disappointing in treatment.

Sir WILLIAM WILLCOX thought that chronic sepsis played an important part in the development of the disease. Dr. PARKES WEBER felt that many cases were overlooked owing to failure to examine the blood. DR. J. F. WILKINSON described one case where sensitivity to pyramidon was readily demonstrated, and another which showed a myelocyte crisis and prompt improvement on treatment with pentnucleotide.

2 p.m. to 3 p.m.

Demonstration of Clinical Cases at the Medical Society of London and the Royal Society of Medicine.

3 p.m.   *Afternoon Session*

1. PROFESSOR A. E. NAISH and DR. T. E. GUMPERT (introduced) described *A Case of von Gierke's Disease.* Typical features were present—a greatly enlarged liver, fasting hypoglycaemia, persistent ketonuria, an abnormal glucose tolerance curve and lack of elevation of the blood-sugar on injection of adrenalin. In addition the faeces were found to contain enormous quantities of starch—a finding that has not hitherto been described. It was suggested that not only is the break-down of liver glycogen interfered with in this condition, but that the digestion of starch in the intestine is also impaired. Possible mechanisms were suggested.

DR. PARKES WEBER compared von Gierke's disease with the fatty infiltration of the liver in rickets. DRS. N. MORRIS and TIDY agreed that von Gierke's disease was one of a large and important group of diseases in which the storage metabolism was disturbed.

2. DR. A. F. HURST described the criteria upon which a diagnosis of *Small Intestine Diarrhoea* can be made. The stools have the characteristics of the discharge from an ileostomy, being watery in contrast with the porridgy faeces from a caecostomy and in colitis, and they contain slight excess of fatty acid crystals. The X-rays show that the caecum is reached within an hour or two of taking a meal. Mucus, which may contain epithelial cells, leucocytes, and red corpuscles, according to the degree of inflammation, indicates that enteritis as well as small intestine irritability is present. A strict ulcer type of diet is required, not the full, but residue-free, diet suitable for colitis.

DR. LEYTON had found dextrose solution by mouth of great value in the treatment of enteritis.

3. SIR WILLIAM WILLCOX reported *Three Cases of Toxic Kidney with Prolonged Suppression of Urine* from carbon tetrachloride, dial and mercuric chloride respectively. The carbon tetrachloride poisoning arose from the use of a Pyrene fire extinguisher in a confined space, and in spite of eleven days' anuria the patient recovered completely. Three other similar cases occurred, one of which was severe and had uraemic convulsions. The second case described was remarkable in that death from uraemia and cardiac failure followed the relatively small dose of 13½ grains of dial. In the third case over 50 grains of mercuric chloride were taken by mistake, but recovery occurred in spite of eight days' suppression of urine, colitis, and stomatitis. A fourth case was

described in which suppression of urine followed the injection of sterilized glycerine into the umbilical cord for retained placenta; in spite of nine days' complete anuria complete recovery occurred.

4. PROFESSOR F. LANGMEAD, with C. G. BARNES and R. I. N. GREAVES (introduced) contributed a short paper on *Spontaneous Overbreathing Tetany*. After discussing the aetiology of this condition they described two typical cases of the syndrome. In these cases the blood chemistry was normal during tetany, but a fall occurred in the calcium of the cerebrospinal fluid. The authors suggest that in all cases of tetany associated with alkalosis there is a drop in the ionized calcium of the blood, manifested by a drop in the total calcium of the cerebrospinal fluid.

5. SIR JAMES PURVES-STEWART demonstrated *Iodo-Ventriculograms of the 3rd and 4th Ventricles*, together with the foramen of Munro, the optic recess, the infundibular recess, and the aqueduct of Sylvius. The opaque fluid was also visible in the interpeduncular cistern in direct continuity with the descending horn of the lateral ventricle. This latter fact supports the view of Merkel and Mierzedjewski, who describe a cleft in the pia mater in the great transverse fissure of the brain, leading into the descending horn, analogous to similar channels in the pia mater of the roof of the 4th ventricle. The existence of this cleft has been disputed by some other anatomists. Iodo-ventriculograms of this sort require a specially rehearsed technique, as the heavy oil rapidly escapes, within a few minutes, from the cranium and descends into the spinal theca.

DR. HURST inquired as to the fate of the injected iodine.